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Original Communications

THE ANATOMY AND HISTOLOGY OF THE SACROUTERINE LIGAMENTS

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IN CONSIDERING the uterine supports and the problem of malposition of this organ, one is immediately concerned with the so-called "ligaments of the uterus." What is the tissue component of these structures and are they truly of any supportive significance? The sacrouterine ligaments are frequently mentioned in textbooks and current literature, but little specific work has been done on them. In reviewing the literature pertaining to uterine support certain significant articles were encountered; however, it can be seen that there is an ever continuing controversy about the supportive tissues of the uterus. As many conclusions have been reached as there are investigators in the field.

The modern concept of uterine support is concerned with the musculofascial tissues within the pelvis. Mackenrodt,[1] Deaver,[2] Montgomery,[3] and Fothergill[4] did much of the early work in demonstrating and describing the various tissue elements found in the parauterine structures. Blaisdell and Somers[5] conducted an extensive study into the anatomy of the sacrouterine ligaments. In 1936, Mengert[6] performed an experiment which to him demonstrated that the sacrouterine ligaments had slight supportive action but that the primary supportive structures of the uterus were the lower parametrial and upper paravaginal tissues.

By virtue of their location, course, attachment, and reported fibromuscular components, the sacrouterine ligaments should be an important factor in holding the cervix upward and posterior. Thelander[7] came to the conclusion that these ligaments were the most important factor in preventing or correcting prolapse. Blaisdell[5] attributed a levator action to these structures, and the Brazilian workers, Oria[8] and Frankel[9] concurred in this idea. The sacrouterine ligaments have also been shown to be involved in neoplastic and inflammatory processes.

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The part they play in uterine retrodisplacement has been studied by Molin and Condamin[10] who have also discussed the sectioning of the sacrouterine ligaments in gynecological surgery.

Anatomical and Histological Study of the Sacrouterine Ligaments

Because of the great divergence of opinion concerning their value it seemed desirable that a study be carried out to demonstrate the actual anatomy and histological components of the sacrouterine ligaments. By such a study it was hoped that the supportive action and surgical utility of these structures could be demonstrated.

The material for this study was obtained in the autopsy room of the University of Michigan Hospital and in the anatomy dissecting laboratories of the University of Michigan Medical School. A total of thirty-three cadavers was

TABLE I. AGE, RACE AND SOURCE OF CASES STUDIED

	NUMBER OF PATIENTS
Age of patients (years)	
0 through 21	5
22 through 45	8
46 through 69	20
Race of patients	
Caucasian	28
Negro	5
Oriental	0
Source of material	
Autopsy	23
Anatomy laboratory	10

observed (Table I), ten being partially preserved and in the dissecting laboratories, while twenty-three were fresh specimens coming to autopsy. They ranged in age from 2 days to 69 years. The majority of the specimens fell into the group over 45 years, the age of prolapse. Eight, though, were younger than 45 but over 22, or in the reproductive age. Five were 22 and younger, and of these two were neonatal deaths occurring in the first three days of life. Thus, representatives of all ages were studied and their structures compared through the various stages of development and degeneration. Of the thirty-three cadavers, twenty-eight were Caucasian and five were Negro.

A sketch was made of each pelvis as observed from above after the abdomen was opened and the intestines removed from the field without distorting the pelvic organs. Another sketch was made after the uterus was placed on an anterior-upward stretch. More detailed drawings were made of cases exemplifying each type observed. Special attention was given to the postcervical structures, and the degree of sacrouterine ligament prominence was noted before and after tension was applied to the uterus. Other special conditions such as uterine pathology, adhesions, uterine position before distortion, adnexal pathology, etc., were recorded. It is interesting to note that in the thirty-three cases observed, thirteen (39.4 per cent) showed pelvic adhesions involving the uterus. Three of these had but a few adhesions while ten were involved in an extensive process. The uteri observed exhibited a variety of pathological conditions other than adhesions. Nineteen (57.6 per cent) of the thirty-three were normal for the age of the patient, and fourteen (42.4 per cent) showed some form of disease (other than adhesions). Of the abnormal conditions observed, the most frequent was leiomyoma, eight cases. Carcinoma of the uterus was found in one case. The other five abnormal uteri showed: one, six-month pregnancy; two, subtotal hysterectomies; one, infantilism; and one, cervical polyp.

If a specimen of ligament was removed for histological study its location was indicated on the drawing of that cadaver. The ligaments were partially or totally removed in twelve cases. These specimens were sectioned longitudinally and crosswise and subjected to various staining techniques. Both the right and left ligaments of the various age groups were examined in longitudinal and cross-section planes at all levels. Complete dissection of the ligaments was carried out in five of the cases, and the nerves, blood vessels, and lymphatics found therein were traced.

Other gross characteristics and tissue components were described. As the position of the uterine corpus was noted both in the anterior-posterior and lateral directions before it was disturbed, one can get an idea of the incidence of retro- and lateral uterine displacement. In this series eleven (33.3 per cent) uteri were in the normal anterior position, ten (30.3 per cent) were in mid-position (in front of sacral promontory), and ten (30.3 per cent) were in various stages of retrodisplacement. Two (6.1 per cent) were surgically absent. It was found that eighteen fundi (54.5 per cent) were in or near the midline. Three (9.1 per cent) were significantly deviated to the right and ten (30.3 per cent) to the left of the midline.

Gross Anatomy.—

Upon gross examination, without distorting the pelvic organs, it was found that of the thirty-three cases seventeen left and fourteen right sacrouterine ligaments were not discernible. Eight left and twelve right ligaments were demonstrable to a minimal degree, while seven left and six right were present to a moderate degree. Only one left and one right ligament were prominent in their appearance (Table II). On the other hand, when anterior-upward tension was applied to the uterus, thus placing the sacrouterine ligaments on a stretch, 71 per cent of the ligaments increased in prominence. Of the 29 per cent which did not become more prominent, all but two could be explained on the basis of uterine pathology, adhesions, adnexal pathology, or prominence before tension was applied.

TABLE II. PROMINENCE OF SACROUTERINE LIGAMENTS BEFORE AND AFTER TENSION IS APPLIED

	LEFT SACROUTERINE LIGAMENT		RIGHT SACROUTERINE LIGAMENT		COLLECTIVELY
Not demonstrable	17	25 (76%)	14	26 (79%)	51 (77%)
Present minimally	8		12		
Present moderately	7	8 (24%)	6	7 (21%)	15 (23%)
Prominent	1		1		
Unchanged with tension	11		8		19 (29%)
Made more prominent	22		25		47 (71%)

Age, race, and source of material must be considered as influencing the prominence of these ligaments before tension was applied. Of the fifteen ligaments observed to be moderate or prominent in their appearance, nine (60 per cent) fell into the age group over 45 years. The remaining six (40 per cent) were in the age group of over 22 but under 45 years. These fifteen ligaments were found in nine different individuals: two (22.2 per cent) were Negro and seven (77.8 per cent) were Caucasian. Six (66.7 per cent) were dissecting laboratory specimens while three (33.3 per cent) were fresh autopsy cases. This latter fact may be of importance in giving a falsely high incidence of prominent or moderately prominent ligaments. For, with fixation and an increased time after death before examination, drying and distortion may have occurred. This demonstrates that for the most part the sacrouterine ligaments are grossly potential only in nature and will increase in prominence with tension unless prevented from so doing by some pathological condition.

These ligaments are attached to the posterolateral aspect of the cervix at the level of the internal os. There are fibrous attachments from the anterior third of the ligaments which course downward to attach to the lateral vaginal fornicies. Near the cervix the sacrouterine ligaments are definite bands of peritoneum-covered tissue, but as they course posteriorly, forming the superior boundary of the cul-de-sac of Douglas, they become thinned out with less definite ridging of the overlying peritoneum. The posterior third of the ligament is fan shaped and composed of more delicate strands of tissue which become attached to the presacral fascia opposite the lower portion of the sacroiliac articulation. The overlying peritoneum is continuous with that covering the rectum; therefore, on the left the sacrouterine ligament is usually apparent along only its anterior two-thirds because of the normal left-sided deviation of the bowel upon its entrance into the pelvis. This further gives an apparent greater prominence to the right sacrouterine ligament after tension is applied to the uterus and a more frequent deviation of the uterus without induced tension toward the left.

If the uterus is pulled to one side of the pelvis, the contralateral sacrouterine ligament assumes a greater prominence and the peritoneum is thrown into multiple radiating ridges directed from the ligament posteriorly, both laterally toward the pelvic wall and downward into the cul-de-sac. This is due to an attachment between the peritoneum and the underlying ligamentous tissue meshwork.

At the cervical end of the ligaments there is a very rich blood supply; this is composed mainly of branches from the uterine vessels. Laterally these vessels become fewer in number and smaller. In the intermediate third the vessels are present to a moderate degree and in the posterior third to a still lesser extent. In the posterior two-thirds they consist of anastomosing branches of the uterine and hemorrhoidal systems.

The nerve components of these ligaments are often difficult to identify grossly. Parasympathetic nerve fibers from sacral two, three, and four segments can be found running in the intermediate and anterior thirds of the ligaments. These form the parasympathetic autonomic innervation of the pelvic organs. At the cervical attachment of the ligaments there can be found sympathetic fibers which have reached the cervix accompanying the uterine artery, and these make up the sympathetic autonomic innervation of the uterus.

There are also lymphatic chains located in these postcervical ligaments. They drain the cervix and lower uterine body toward the sacral nodes which in turn send efferent lymphatics to the common iliac and perilumbar chains of nodes. The lymphatic pathway may become quite prominent with regional inflammation or carcinomatous metastases from the cervix.

Microscopic Anatomy.—

In demonstrating the histological components of the sacrouterine ligaments various staining procedures were utilized. The common hematoxylin and eosin (H. & E.) stain was used on each specimen, and it was found that this is the best for general tissue identification; but, even with thin sections of tissue properly stained, it was impossible positively to differentiate loose fibers or bundles of smooth muscle from dense fibroelastic connective tissue. Therefore, special differential staining techniques were utilized. Of these the van Gieson stain was ideal in giving contrasting stain to connective tissue and smooth muscle. With this process the muscle takes a yellow to brownish-yellow color while the connective tissue becomes a deep red to purple. The Masson trichrome staining technique also was found to be helpful in differentiating these tissues. This imparts a green color to the connective tissue and a pink or red hue to the smooth muscle. The elastic elements of the connective tissue can be brought out by use of the Weigert technique.

Sections of the ligaments were removed from both sides and at many levels for study of the cross-section histology. In other cases the ligaments were cut longitudinally along part or all of their course. In Case 30, a 22-year-old girl who died with glomerulotubular nephritis, both sacrouterine ligaments were removed in toto, including a portion of the cervix with the ligamentous attachment and all tissue back to and including the fibrous attachments with the presacral fascia (Fig. 1). The sacrouterine ligaments have been placed under tension by pulling the uterus upward and forward. On this drawing have been shown the various levels of the ligaments which were extensively studied and which are illustrated by subsequent photomicrographs.

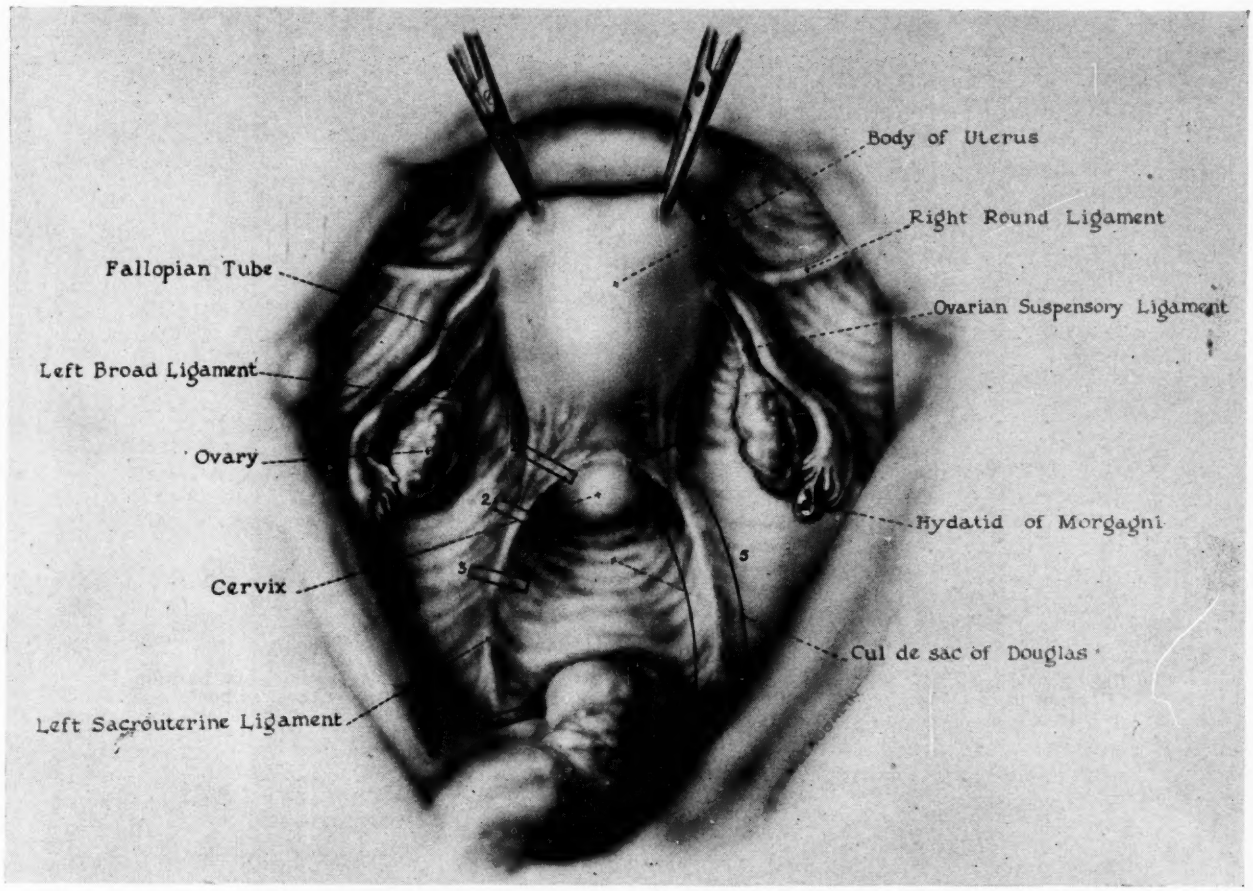

Fig. 1.—Case 30, showing pelvic organs and ligaments with uterus placed on anterior-upward tension.

The entire ligaments of Case 30 were fixed in 10 per cent formaldehyde and then imbedded in paraffin in their normal relationship (Fig. 2). Because of the technical difficulties in handling such large sections, they were bisected and, after cutting and staining, mounted on a large slide (4 by 5 inches) in their original relationship (Fig. 3). Due to compression of the tissues between two glass slides to prevent curling during fixation, the ligaments appear to be much wider than is the true condition. The actual extent of the ligament has been outlined on the picture which illustrates the right sacrouterine ligament.

The right side of Fig. 1 shows the area included in the section shown in Fig. 3. The left side shows the levels at which tissue was removed for cross-section study in other cases. It must be noted that sections were removed from both sides in different cases for longitudinal and cross-section study at various

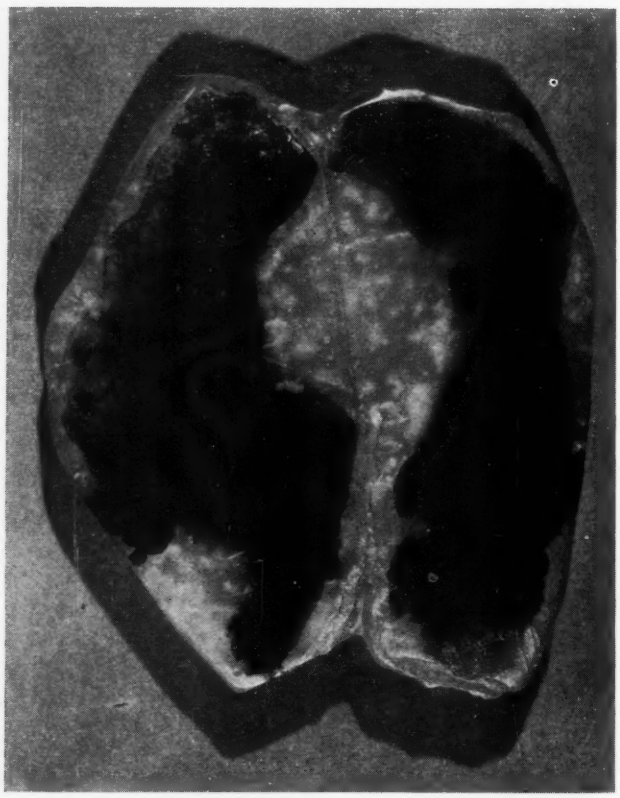

Fig. 2.—Sacrouterine ligaments of Case 30 mounted in their normal relationship in paraffin prior to sectioning. The cervix would be located at the upper aspect of the ligaments.

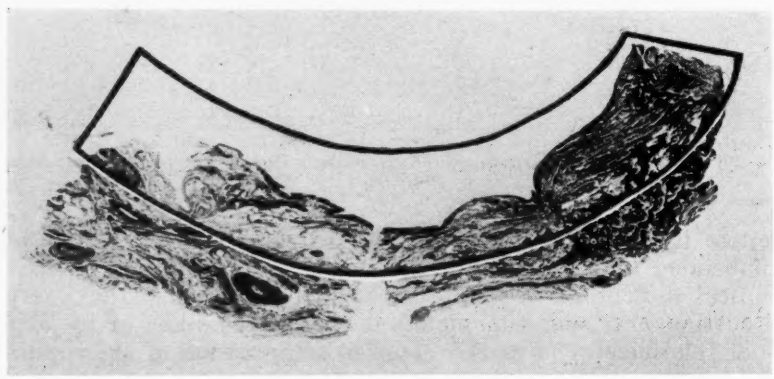

Fig. 3.—The right sacrouterine ligament cut longitudinally and mounted on a large slide for microscopic study. Outlined area is true extent of ligament (see text). This is area shown in 5 of Fig. 1 and is the right ligament of Fig. 2. (H. & E. stain, ×1.)

levels, but for the sake of illustration the cross-section levels are indicated on the left while the longitudinal section is shown on the right. A few photomicrographs are shown of these various levels. Many other serial blocks of tissue were removed and studied, but it is impossible to show illustrations of them all.

Fig. 4.

Fig. 5.

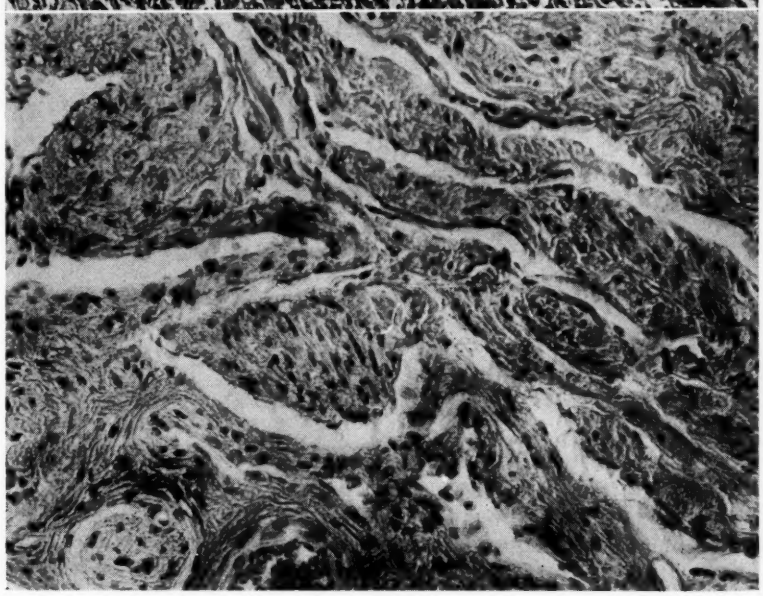

Fig. 4.—Cervical attachment of sacrouterine ligament. Area 1 of Fig. 1. Darker areas are connective tissue while remainder is chiefly bundles of smooth muscle. Note vessel-nerve group in lower right corner. (Cross section, van Gieson stain, ×75.)

Fig. 5.—Same area of cervical attachment as shown in Fig. 4 under high power. This shows the preponderance of smooth muscle and the abundance of blood vessels. (Cross section, H. & E. stain, ×225.)

It is best to proceed in an orderly fashion in examining the tissue components present in these ligaments, starting at the cervix and proceeding posteriorly to the sacrum. The cervical attachment (Fig. 4) was found to be made up of closely packed bundles of smooth muscle, continuous with the uterine musculature, with an interweaving connective tissue meshwork. There are abundant medium-sized and small blood vessels and small nerve bundles. With the H. & E. stain one gets the impression that there is more smooth muscle than can be proved to exist by the differential stains. Even with the special stains, however, smooth muscle can be shown to be the predominate tissue component at this level. The van Gieson stain and Masson stain reveal this tissue differentiation to good advantage. Longitudinal sections of the same area show the abundant smooth muscle fibers cut lengthwise. Under high power with the H. & E. stained tissue one cannot definitely tell the extent of smooth muscle and connective tissue fibers. Fig. 5 is the same tissue as Fig. 4, but here we do not have the benefit of the differential stain. Nevertheless, there is apparently a great preponderance of smooth muscle at this level. Much of it is located in vessel walls, but other dense bundles can be demonstrated.

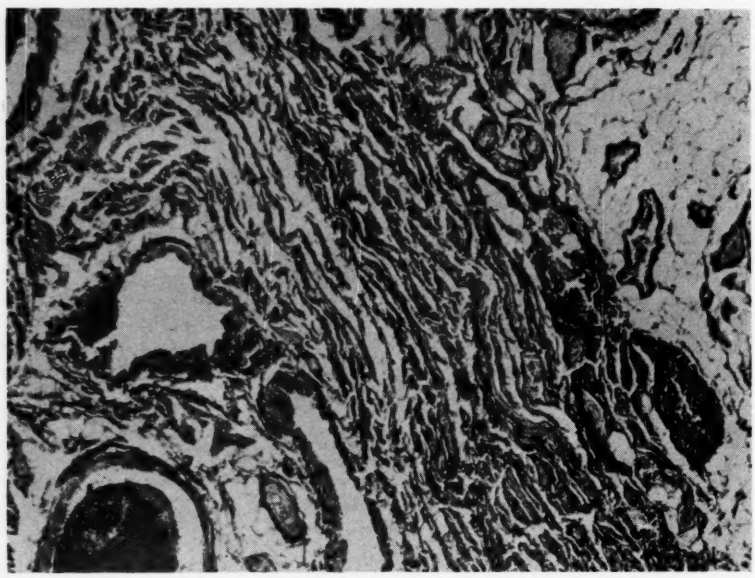

Fig. 6.—Junction of the anterior and middle thirds of the sacrouterine ligament. The left is more superficial. This is area 2 of Fig. 1. There is a parasympathetic ganglion along the right upper edge. (Cross section, van Gieson stain, ×75.)

As we proceed posterolaterally the smooth muscle diminishes in amount and the connective tissue becomes denser and more prominent. Small and medium-sized arteries and veins are prominent throughout the anterior third of the ligament, but become less so as the intermediate third is reached. Nerve elements become more grouped and individual nerves are larger more distal to the cervix. Parasympathetic ganglia appear in sections taken 3 to 4 cm. posterolaterally to the cervix in some cases as can be seen in Fig. 6 taken at this level. In other cases these ganglia can be seen to be located as far distal to the cervix as the junction of the middle and posterior thirds of the ligament.

In the intermediate third (Fig. 7) of the ligament the predominate tissue component is connective tissue. There is a dense layer of collagenous connective tissue underlying the peritoneal serosa to which is given the name "stratum fibrosum." This is thicker in the sacrouterine ligament than in adjacent areas.

High-power photomicrograph of this layer (Fig. 8) shows it to be made up chiefly of dense collagenous connective tissue. Only a few scattered smooth-muscle fibers can be demonstrated by special stains in this layer. Beneath the stratum fibrosum can be found a loose areolar connective tissue and fat through which course a moderate number of vessels, the parasympathetic nerves and

Fig. 7.

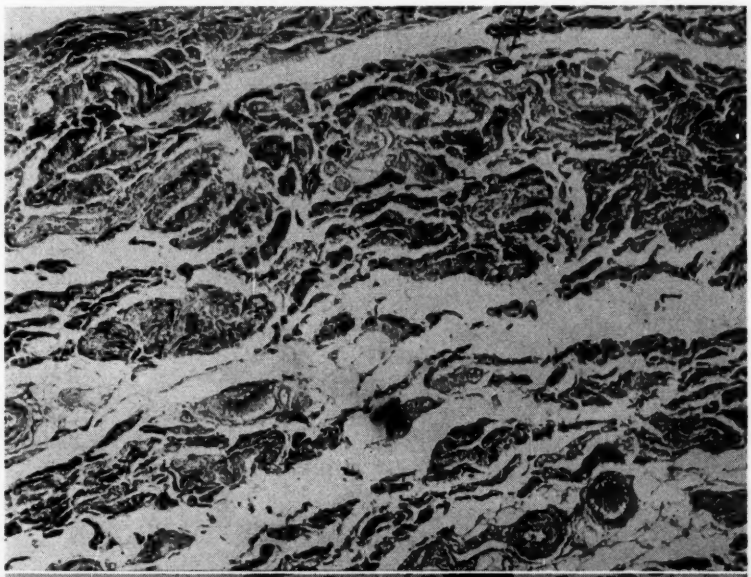

Fig. 8.

Fig. 7.—Middle third of ligament with peritoneal surface in upper left corner. Condensation of connective tissue into stratum fibrosum. This is area 3 of Fig. 1. Note abundant small and medium-sized vessel. (Cross section, van Gieson stain, ×75.)

Fig. 8.—High power of the stratum fibrosum, same area as Fig. 7. This is composed chiefly of dense bundles of collagenous connective tissue with a few intermingling fibers of smooth muscle. The peritoneal surface is in the upper left portion of the picture. The serosal layer was destroyed in processing. (Cross section, van Gieson stain, ×225.)

their ganglia, the lymphatic chain to the sacral nodes, and a few isolated bundles of smooth muscle. With differential stains there is on low-power microscopic examination apparently an abundance of smooth muscle, but upon close observation this can be found to be mainly in the walls of the blood vessels. Nevertheless, there are a few isolated muscle bundles in this region. The connective tissue located beneath the stratum fibrosum is in the form of a loose meshwork and does not form a distinct fibroelastic band or bundle.

Fig. 9.—Intermediate third of the sacrouterine ligament sectioned longitudinally. Note condensation of connective tissue into stratum fibrosum and the less dense deeper tissue meshwork. (H. & E. stain, ×75.)

Fig. 10.—Sacral attachment of the sacrouterine ligament. Dense band at left is presacral fascia with a few attached fibers of the piriformis muscle. Loose connective tissue and fat form the distal end of this postcervical ligament. (Cross section, H. & E. stain, ×75.)

Fig. 9 shows the intermediate third of the ligament in another case sectioned longitudinally. Here the stratum fibrosum is very apparent and the peritoneal serosa has been maintained. This tissue comes from an autopsy specimen and emphasizes the well-known fact that fresh tissue properly fixed soon after death is superior for microscopic examination.

The posterior or sacral third of the sacrouterine ligament is composed almost entirely of loose strands of fibroelastic connective tissue and surrounding fat (Fig. 10). Filaments of this connective tissue are attached to or become continuous with the presacral fascia. Sections taken at this attachment also show the adjacent piriformis muscle fibers which originate from the sacrum and run through the greater sciatic notch to become attached to the greater trochanter of the femur. In this posterior third, blood vessels, lymphatics, and nerve fibers are present only to a minimal degree; and smooth muscle is completely absent except in the vessel walls. At the sacral attachment the peritoneal covering is lacking as it has been reflected over the rectum. The microscopic sections bear out the gross appearance of thin filaments of tissue radiating in a fanlike pattern from the more anterior portion of the ligament toward the sacrum. Some of these filaments can be seen to attach to the peritoneum above and below the ligament proper.

Summary

To determine the gross and microscopic anatomy of the sacrouterine ligaments as well as their physiology and clinical significance, a review of the literature and an anatomical study were undertaken. Many articles refer to these ligaments, but little specific work has been done on them. Mainly they are mentioned secondarily as uterine supports or pertaining to the correction of uterine malposition. The studies which have previously been done leave the nature of these ligaments in a confused and controversial status. However, from the literature it may be concluded that the main supportive structures of the uterus are the parametrial and paravaginal musculofascial tissues, and that the sacrouterine ligaments are secondary in supportive action. Functionally the sacrouterine ligaments act to hold the cervix upward and posteriorly. Clinically these ligaments may be helpful in a differential diagnostic respect as well as being involved in certain pathological processes. Various surgical procedures have been directed toward these structures, some primary and others secondary to other procedures in the pelvis.

An attempt was made to determine the actual anatomical configuration and histological components of the sacrouterine ligaments. To do this the pelves of thirty-three cadavers were studied. Ten of these were partially preserved dissecting laboratory specimens while the remainder were autopsy material. Thorough dissections of the ligaments and their contained structures were carried out in five cases. Drawings were made of each case: first, before the pelvic organs were disturbed, and second, after the sacrouterine ligaments were placed under tension. The entire ligaments or blocks thereof were removed for microscopic examination in twelve cases, and various staining techniques were utilized to demonstrate the tissue components.

To summarize the gross and microscopic anatomy of the sacrouterine ligaments it may be said that they are bands of tissue coursing from the cervix around the inlet of the pouch of Douglas to become attached to the sacrum.

Grossly they are often merely potential ligamentous structures. Histologically they may be divided into thirds. The anterior or cervical third contains in order of prominence (Table III) smooth muscle, fibroelastic connective tissue, blood vessels, nerves, and lymphatics. The intermediate third is made up of

TABLE III. HISTOLOGICAL COMPONENTS OF THE SACROUTERINE LIGAMENTS IN ORDER OF THEIR PROMINENCE

	HISTOLOGICAL COMPONENTS BY REGIONS
Cervical (Anterior third)	Smooth muscle Connective tissue Blood vessels Nerves (Sympathetics and parasympathetics) Lymphatics
Intermediate (Middle third)	Dense connective tissue (stratum fibrosum) Loose connective tissue and fat Nerves and ganglia (parasympathetic) Blood vessels Smooth muscle Lymphatics
Sacral (Posterior third)	Loose connective tissue and fat Blood vessels Nerves and lymphatics

connective tissue concentrated in a subserosal stratum fibrosum and scattered in the deeper zone as a less dense meshwork. Nerve elements are numerous and blood vessels are moderately prominent. There are also a few scattered strands of smooth muscle in this region, and lymphatics may be present to a variable extent. The posterior or sacral third is composed almost entirely of loose strands of connective tissue and intermingling fat. There are a few vessels, nerves, and lymphatics located here.

There is no reason why, if the sacrouterine ligaments are well developed, they should not be utilized in such operations as vaginal hysterectomy, enterocele correction, uterine retroversion, and prolapse; but they should not be credited with undue supportive value. The anterior or uterine end of the ligament may be, and often is, well developed. This has led to the opinion that these ligaments have more supportive action than this study would appear to justify, due to the weak and insignificant development of the posterior aspect. The old addage that a chain is no stronger than its weakest link can aptly be applied here, for the supportive action of the posterior third of the ligament is certainly questionable.

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PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA*

A Clinicopathological Study of 476 Cases

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PREMATURE separation of the normally implanted placenta has been regarded as potentially the most dangerous form of obstetrical hemorrhage occurring in the last trimester of pregnancy. In 1776, Rigby[1] was the first to distinguish between cases of placenta previa and premature placental separation as the cause of third trimester bleeding. At the time, he designated the cause of the latter as "accidental" hemorrhage in contrast to the "unavoidable" type occurring with placenta previa. Goodell[2] in 1875 called attention to the high mortality in patients with premature separation of the placenta. Chantreuil[3] in 1801 first noted its association with albuminuria which was thought by Winter[4] in 1885 to be associated with nephritis. Holmes[5] in 1901 described 200 cases and suggested the name "abruptio placentae" for the severe type in which there were abdominal signs and symptoms associated with concealed hemorrhage. Bartholomew,[6] Beavers,[7] Polak,[8] and Dieckmann[9] attempted to classify their cases with emphasis on the clinical picture presented. Irving[10] classified his cases as those with external hemorrhage and those with internal or concealed hemorrhage. He concluded that the retention of blood within the uterus is of more importance with regard to the possibility of a fatal outcome than the coexistence of toxemia. Kellogg in collaboration with Hertig[11, 12] proposed a pathological classification which was not correlated with the clinical course of the patients.

Material and Results

This wide variation of opinion is indicative of the confusion which exists regarding the many factors which produce this complication. Hence, it was thought desirable to review the experience at the Boston Lying-in Hospital in the hope of clarifying the relationship of the clinical and pathological aspects of cases of premature separation of the placenta. During the period studied, from 1931 to 1946, inclusive, there were 476 cases of premature separation of the normally implanted placenta associated with 40,547 deliveries, an incidence of 1 in 85. It was hoped that from a correlative study of this material a universal pathological and clinical classification could be devised which would prove useful in future studies of this complication.

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The clinical diagnosis of premature placental separation was established by the following signs and symptoms, namely, occurrence of sudden abdominal pain, some degree of uterine tenderness due to concealed hemorrhage and the presence of external vaginal bleeding with or without shock. The diagnosis of placenta previa was excluded by the usual clinical methods. A few patients in this study showed no clinical evidence of premature separation of the placenta but the placenta on examination revealed sufficient areas of recent adherent blood clot, often associated with infarction, to warrant a pathological diagnosis of premature separation. In classifying these cases they were first separated into two groups called toxic and nontoxic depending upon the presence or absence, respectively, of albuminuria and hypertension. In each of these groups there were a number of subgroups (Table I). In the nontoxic group there were 276 cases, an incidence of 1 in 133 deliveries. In the toxic group there were 200 cases in 3,654 patients who had either associated hypertension or proteinuria or both, an incidence of 1 in 18.3 such pregnancies. It seemed advisable not to introduce any new terms in the subgrouping of the toxic cases but to use the terms describing hypertensive and albuminuric pregnancies as proposed by the Committee on Maternal Welfare.[13] Hence, beginning in 1935, all toxemic pregnancies were diagnosed according to this classification. The records used from 1931 to 1946, inclusive, were regrouped according to this classification and hence a comparison could be made between mild and severe pre-eclampsia and eclampsia during this sixteen-year period.

TABLE I. CLASSIFICATION OF PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA

	SEPARATION		
	CLINICAL	PATHOLOGICAL ONLY	TOTALS
I. Nontoxic, Idiopathic.—			
A. Decidual, trophoblastic degeneration only	137	3	140
B. Abnormalities of placental development			92
1. Circumvallate	82	0	
2. Absolute or relative short cord, marginal insertion of cord	8	0	
3. Succenturiate placenta	2	0	
C. Rupture of marginal sinus	32	0	32
D. Excessive intrauterine pressure (polyhydraminios, multiple pregnancy)	9	0	9
E. Trauma	3	0	3
Total			276
II. Toxic.—			
A. Without antecedent vascular and renal disease			187
1. Grade I	83	12	
2. Grade II	54	5	
3. Eclampsia	1	32	
B. With antecedent vascular and renal disease only			2
1. Vascular, essential or malignant hypertension	1	0	
2. Renal, glomerulo- or pyelonephritis	1	0	
C. Combination of A and B			11
1. Vascular disease with superimposed toxemia	4	0	
2. Renal disease with superimposed toxemia	7	0	
Total			200

A description of the pathological processes from which were evolved the various subgroups within the classification is presented.

I. Nontoxic, Idiopathic Group.—Some degree of trophoblastic degeneration and necrosis of the decidua are consistent findings in the placentas of normal

pregnancies, particularly during the last trimester. In cases of premature separation this same process is present. There are areas of cystic, moth-eaten degeneration beginning at the trophoblastic decidual junction of either the placental septa or site. It has been suggested by Hertig[12] that the "integrity of the vascular supply to the placenta depends upon the integrity of the placental site rather than upon any intrinsic strength of the vessels themselves. It then becomes evident that dissolution of the placental site will result in rupture of the decidual sinusoids leading to placental separation." This tendency toward regression of the supporting structure of the placental site must be important in producing placental separation. Any interference of the uterine arterial supply to the placental site may aggravate this process. However, in the absence of a known specific cause for this change the etiology must be considered at the moment idiopathic in nature.

In spite of a specific cause there are factors which appear to play a contributing role. Circumvallate placenta is a relatively common abnormality of placental development which may initiate the production of premature separation by the degeneration of the trophoblastic decidual areas which are in association with the invasion of the decidua vera by the "extrachorionic" margin of the circumvallate placenta.

Absolute and relatively short umbilical cords are found in normal placentas. Here placental separation may occur due to a mechanical reason such as undue tension on the cord at the time of external version.

Rupture of the marginal sinus of the placenta, aggravated by the degeneration of the decidual trophoblastic junction, is a frequent anatomical cause of premature placental separation in this nontoxic group.

An additional small group is composed of patients in whom separation occurs because of the above degenerative process combined with a sudden decrease in intrauterine pressure. Examples of this would be spontaneous rupture of the membranes in the presence of marked polyhydramnios or multiple pregnancy.

For completeness trauma is included, but its importance as an initiating factor in premature placental separation has been overestimated. Actually it is very infrequent.

II. Toxic Group.—The underlying pathological process was found to be quite similar to that seen in the nontoxic group, namely, degeneration or necrosis of the trophoblastic decidual junction. In addition there were changes within the arterioles of the placental site originally described by Williams[14] in 1915 and illustrated by Hertig[12] in 1945 as acute atheromas of these decidual vessels. These lesions may lead to partial or complete obliteration of the lumen with subsequent necrosis of the surrounding decidua, followed by hemorrhage.

From this study it was hoped that if there were any decidual vascular lesions peculiar to the placental separation in patients with hypertension and albuminuria, careful review of the pathological material might reveal the type of pregnancy toxemia in which these changes occurred. We were particularly interested in searching for causes such as decidual arteriolar vessel changes which might explain the occurrence of a higher incidence of premature separation in this toxic group. In the 174 cases in which microscopic material was available for study, only seven cases showed any evidence of such a decidual arteriolar lesion, i.e., acute atherosis. It is interesting and, perhaps, highly significant that these lesions of the placenta occurred in patients who prior to pregnancy had established vascular or renal disease.

A microscopic study of the toxic cases of premature placental separation did reveal a correlation between the incidence of placental infarction and the tendency of the placenta to separate as shown in Table II.

TABLE II. RELATION OF PLACENTAL INFARCTION TO TOXIC SEPARATION

	PRE-ECLAMPSIA		ECLAMPSIA	
	NO. CASES	PER CENT	NO. CASES	PER CENT
Premature separation with red and/or white infarcts	85	60.2	22	66.67
Premature separation without infarction	32	22.7	11	33.3
Infarcts only	12*	8.5	0	0
No infarcts	12*	8.5	0	0
Totals	141	99.9	33†	99.97

*Clinical separation only.

†There were 36 cases of eclampsia not included in this study, in which placental sections showed neither separation nor infarction.

Fetal Mortality.—As might be expected, fetal mortality was high in these cases of placental separation. Fetal loss in the nontoxic group was 34 per cent, with 101 stillbirths or neonatal deaths in the 276 pregnancies. There were actually 290 births with fourteen sets of twins, a much higher incidence of multiple pregnancy than usual, and this must be a factor in producing placental separation. The fetal mortality in the toxic group was 52 per cent. In Table III is listed the fetal mortality in the varying degrees of toxemia of pregnancy during this period without and with complicating premature placental separation.

TABLE III. FETAL LOSS IN TOXEMIA

GRADE OF TOXEMIA	WITHOUT SEPARATION		WITH SEPARATION	
Mild (Grade I).—				
Total cases	3,141		95	
Fetal loss	219	7%	40	43%
Severe (Grade II).—				
Total cases	423		59	
Fetal loss	114	27%	35	65.6%
Eclampsia.—				
Total cases	36*		33	
Fetal loss	18	50%	20	70%
Total number cases	3,633*		187	
Total fetal loss	351	9.66%	98	52%

*There were 21 additional cases of eclampsia during this sixteen-year period but not included in the study because the placentas were not available for study. Hence no statement can be made about the frequency of separation in these cases since in eclampsia this is usually not clinically recognized.

Maternal Mortality.—There were fifteen maternal deaths, three associated with nontoxic and twelve with toxic premature placental separation.

Nontoxic: Two of the maternal deaths in the nontoxic group were due to severe bilateral bronchopneumonia (influenzal type) and acute pyelonephritis with *E. coli* bacteremia and uremia, respectively. In both of these cases, spontaneous labor ensued after the inflammatory processes had developed. The placentas separated during the second stage of labor and were only incidental to the cause of death in these patients.

The third maternal death occurring in the nontoxic group was in a patient, 27 years of age, gravida v, para 0, with a past history of several spontaneous miscarriages. At the thirty-third week of her pregnancy she entered the hospital because of pink vaginal discharge. After three weeks' hospitalization, sterile vaginal examination revealed a small cervical erosion and there was no evidence of placenta previa. She re-entered the hospital, two weeks

overdue, with a history of ruptured membranes and not in labor. There was no albuminuria nor elevated blood pressure. Mild labor began twelve hours after admission and because of lack of progress x-ray pelvimetry was thought advisable. While this examination was being done the patient began to have brisk vaginal bleeding, associated with continuous severe abdominal pain. Bleeding continued per vaginam and it was noted that there was some bleeding from the nose and mouth. Although the fetal heartbeat was irregular, an immediate hysterotomy was performed. Recent hemorrhage was observed beneath the peritoneal surface of the uterus. The patient's placenta was found completely separated and an 8 pound, 8 ounce stillborn infant was delivered. Immediately postoperatively the patient's blood pressure dropped to 70/40. The bleeding continued from the mouth. The uterus did not react well to oxytocics. Vaginal bleeding continued, supposedly due to atony of the uterus, and, because of this, immediate hysterectomy was performed. However, the patient expired in spite of adequate blood replacement therapy. Postmortem diagnoses were: abruptio placentae of the nontoxic variety, intraperitoneal bleeding and subserosal bleeding of the anterior peritoneum, as well as petechial hemorrhage of the ureters. Mild bilateral pleural effusions and pulmonary atelectasis were present. Amniotic fluid emboli were present in the uterine sinusoids as well as in the general circulation. Studies performed on the circulating blood revealed an active inhibition of the clotting mechanism.

Toxic: Of the twelve deaths in patients with toxic placental separation, four had eclampsia and were admitted to the hospital as emergency cases in a comatose state. These four patients had pathological evidence of separation but their clinical course was probably little influenced by this occurrence. Excluding these four cases, the case histories of the remaining eight deaths are briefly presented.

CASE 1.—This patient had been examined vaginally without sterile precautions by a local physician prior to hospital admission. She was treated by the designated "conservative method"—namely, artificial rupture of the membranes, cervical and vaginal packing, a tight abdominal binder followed in some instances by the use of uterine stimulants in order to promote labor. She died undelivered fourteen hours following this procedure. Autopsy revealed an extensive *B. welchii* infection.

CASES 2 and 3.—These two patients were admitted to the hospital with clinical signs of severe toxic placental separation and were successfully delivered by rupture of the membranes, vaginal packing, and Pituitrin stimulation of labor. They died of uremia on the seventh and eleventh postpartum days, respectively. Postmortem examination revealed bilateral cortical necrosis of the kidneys as well as typical Couvelaire uteri.[15]

The next two patients in the series were already in the hospital under treatment for pre-eclampsia, one a mild case and one severe.

CASE 4.—This patient developed clinical signs of placental separation forty-nine hours after admission and was treated by the conservative method. She died undelivered twenty-six hours later. Postmortem examination revealed a Couvelaire uterus with cornual subserosal hemorrhages. No doubt the immediate cause of death was toxic premature separation of the placenta, shock, and hemorrhage.

CASE 5.—This patient was a 23-year-old gravida i, thirty-seven and one-half weeks pregnant, who was admitted from the clinic for treatment of severe pre-eclampsia. Seventy-two hours after admission with no improvement in her general condition following 25 per cent glucose intravenously, as well as diethylstilbestrol, 300 mg. daily, labor was induced by artificial rupturing of the membranes through a moderately favorable cervix. Near the end of an eight-hour labor, the fetal heartbeat disappeared and the patient's blood pressure fell from 142/122 to 80/40 with no other clinical signs of shock. A stillborn infant weighing 4 pounds, 14 ounces was delivered easily by low forceps. The placenta and a moderate amount of clotted blood followed immediately. Pathological examination revealed confirmatory evidence of premature separation. She had so-called "explosion" of the soft tissues of the vagina combined with some degree of uterine atony. Repair of the lacerations with vaginal

and uterine packing did not control the bleeding. Hysterectomy was performed because of supposedly increased uterine atony. The uterine arteries were sutured. Bleeding continued from the cervical stump. Resuturing the ovarian vessels was of no avail. Clamps were left on these uterine and ovarian areas without effective hemostasis. In spite of thirty transfusions given, the patient died soon after the operation. No autopsy was performed but examination of the uterus did not reveal subserosal hemorrhage consistent with a Couvelaire uterus. In retrospect an upset in the clotting mechanism was no doubt present.

CASE 6.—This patient was a 25-year-old gravida iii, secundipara, who died undelivered seven and one-half hours after admission, six and one-half hours after the conservative treatment was instituted. At autopsy a Couvelaire uterus was found associated with premature separation of the placenta. There were also periportal necrosis of the liver and thickening of the glomerular basement membrane of the kidney similar to those found in patients dying from eclampsia.

CASE 7.—This patient was a 34-year-old gravida vi, quintipara, near term, with a history of severe headaches six days prior to admission, who entered the hospital with a blood pressure of 124/86. Even though this is an apparently normal blood pressure, it should be considered as evidence of shock in this patient as other clinical signs of premature placental separation were evident. She was treated by the conservative method and died undelivered three hours after admission with questionable diagnosis of pulmonary embolism. There was no autopsy.

CASE 8.—The last patient was a 35-year-old gravida vii, quadripara, thirty-five weeks pregnant, with a past obstetrical history of two previous abortions and three premature deliveries at approximately six and one-half months' gestation and only one living child. She reported to the clinic at twenty-nine weeks with a blood pressure of 138/88, negative albumin and an 11 pound weight gain. She subsequently reported to the clinic complaining of abdominal pain of one week's duration and a blood pressure of 164/94 and 3+ albuminuria. At her insistence the patient went home before hospitalization. Soon after arriving home she had another attack of severe abdominal pain and arrived at the hospital four hours later with a blood pressure of 108/90 and all the signs of severe placental separation. No fetal heartbeat was heard and little external bleeding was evident. She was treated by the conservative method. She bled through the vaginal pack and a small amount of vaginal ooze was continuing at the time of her death twelve hours after admission. There was no autopsy.

The primary causes of death in Cases 1, 2, and 3 were complications which often accompany this disease, namely, puerperal sepsis and bilateral cortical necrosis of the kidney. The latter lesions appear to be irreversible in type and are no doubt produced early in the course of this complication. It is doubtful if any other method of treatment would have altered the clinical course of the patients.

The remaining five fatal cases in the toxic group and the third death occurring in the nontoxic group are of special interest and will be considered in more detail in the discussion of the treatment.

Discussion

Distribution.—The incidence of premature separation varies greatly from clinic to clinic, depending upon the criteria accepted for diagnosis. Davis and McGee[16] reported from the Chicago Lying-in Hospital an incidence of 1 in 244 cases. Various other authors quoted an incidence varying from 1 to 90 (Boulware[17]) to 1 in 350 (Nicholls[18]). In this study the incidence was 1 in 85, a much higher incidence than usually reported. The probable explanation for this is our relatively high proportion of nontoxic cases, namely 58 per cent, and our practice of examining pathologically all placentas associated with complications of labor.

In comparing the nontoxic premature separations with the total number of normal deliveries, an incidence of 1 in 133 cases was found. This large nontoxic

group is due in part to cases with abnormal placental development with or without rupture of the marginal sinus. These two factors, namely, circumvallate placenta and ruptured marginal sinus, have not been stressed sufficiently by others as an etiological factor in antepartum bleeding. (It is of interest that of all the premature circumvallate placentas examined in this sixteen-year period, 38 per cent had pathologic evidence of premature separation.) Many of these patients were in labor when first seen. It suggests that the increased activity of the laboring uterus, in the presence of a placenta whose "extrachorionic" margin is in abnormal relationship to the degenerated decidua, is enough to initiate separation of the margin.

The proportion of toxic premature separation with associated hypertension and proteinuria toxemia (as compared to nontoxic separation) is quoted as 57 per cent (Williams[14]), 24 per cent (Goethals[19]), and 56 per cent (Davis and McGee[16]). In our clinic 42 per cent of the cases of premature separation had some degree of toxemia, with an absolute incidence of one separation in 18.3 toxemic patients. Not only was the frequency of separations of the placenta increased with associated albuminuria and hypertension, but it was increasingly frequent as the toxemia became more severe (Table IV).

TABLE IV. DISTRIBUTION OF PREMATURE SEPARATION AND DEGREE OF TOXEMIA

	TOTAL NO. CASES	NO. WITH SEPARATION	PER CENT	INCIDENCE
Mild pre-eclampsia	3,141	95	3.0	1:33
Severe pre-eclampsia	423	59	13.8	1:7.23
Eclampsia	90	33	36.6	1:2.7
Totals	3,654	187*	5.1	1:19.5

*Excluding 13 cases with essential hypertension and nephritis in which the placentas were separated. (See Table I.)

Pathology.—The gross and microscopic examinations of the placentas from these cases of toxic placental separation show no single pathognomonic lesion other than the hemorrhage into and on the decidua. There are, however, certain pathologic lesions which appear to be correlated with premature separation.

The changes occurring in the coiled arterioles of the placental site are described by Hertig[12] as a "collection of foamy, fat-ladened mononuclear leucocytes or phagocytes," appearing beneath the intima of the coiled arterioles. This represents the early stage of the lesion. It is followed by a fibrinoid degeneration of the media which is "superseded by a fibroblastic proliferation of the intima" which soon results in partial or complete obliteration of the lumen. If the branches of the coiled arterioles which nourish the endometrium as well as supply the placenta with blood become obstructed, there follows necrosis of the surrounding decidua which leads to hemorrhage. This hemorrhage as it increases in severity, detaches the placenta." These lesions, originally thought by one of us (A. T. H.) to be pathognomonic of toxic separation, were associated in this study with seven cases of essential hypertension or chronic glomerulonephritis with superimposed eclamptogenic toxemia. Thus, these vascular lesions are correlated with previous vascular or renal disease rather than with placental separation per se. Of course, many of the microscopic sections did not have decidual arterioles present, so that complete evaluation of this finding was not possible.

Although few cases of toxic separation were found associated with acute atheromas of the arterioles of the placenta, it is probable that these vessels do play a part in premature separation. Perhaps vascular spasm of spiral arterioles, without demonstrable lesions morphologically, may play the major role in premature separation. Certainly more careful microscopic study of the decidual vessels is necessary before definite significance of this lesion can be determined.

Infarction, relatively common in these placentas, may be either the cause or the result of premature placental separation. On the other hand, there may be no correlation between infarction and premature separation. Hence, an area of premature separation interrupts the maternal placental circulation, either arterial or venous, and leads to infarction of the placenta. Since the blood supply of the endometrium beneath the placenta (decidual basalis) is derived from branches of the same sinusoids that supply the placenta, the decidua itself associated with infarcts often becomes necrotic. Such necrosis leads to rupture of associated sinusoids with resultant hemorrhage into the decidua, i.e., premature separation. It must be emphasized that decidual sinusoids, especially venous ones, have little intrinsic strength per se and therefore rupture when the supporting decidual tissue becomes necrotic.

Fetal Loss.—Thirty-one infants in the nontoxic group were delivered by cesarean section with five stillbirths and neonatal deaths, a mortality of 17 per cent. The remaining 259 infants were delivered through the pelvis. In this group there were ninety-five stillbirths and neonatal deaths, a mortality of 37 per cent. No doubt a certain number of these infants could have been salvaged with a more liberal use of cesarean section. However, in this small series delivered by this method, a fetal mortality rate of 17 per cent is no indication that abdominal delivery will insure a living infant.

In the toxic group, the fetal loss increased with the severity of the toxemia. In patients with mild pre-eclampsia without separation, the fetal mortality was 7 per cent. Should premature placental separation occur in this group, the fetal loss was increased more than six times, namely to 43 per cent. In patients with severe pre-eclampsia without separation the fetal loss was 27 per cent. Should premature separation occur, this fetal death rate was increased to 66 per cent. Thus, premature separation adds a constant increment to the fetal mortality, namely, 36 to 39 per cent regardless of the initial degree of toxemia. Thus variations in the fetal mortality are due to the severity of the toxemia rather than to the separation per se.

Maternal Mortality.—Maternal mortality is conceded to be high in this complication of pregnancy. Bland and Rakoff,[20] in a review of twenty-one reports comprising 2,319 cases of premature separation in the literature, found a 6.3 per cent maternal mortality. Davis and McGee[16] found 7.3 per cent. Irving[10] states in an extensive review on the subject that 5 per cent to 10 per cent represents a "fair average for all cases, including both the severe and mild." In the series being reported, the uncorrected maternal mortality was 3.15 per cent.

However, all writers fail to correlate their maternal mortality in relation to the extent of placental separation. Therefore, this arbitrary classification of the degree of placental separation was made in order to analyze our maternal mortality. (See Table V for criteria.) Mild degrees of separation caused no maternal mortality irrespective of the presence of coexisting toxemia. The deaths which occurred had much more extensive placental separation and were classified as moderate to severe in type. These cases all had with one exception (Case 3, nontoxic series) associated toxemia. Table VI correlates the maternal deaths in the toxic series with the degree of placental separation. Correction was made for the four patients with eclampsia in whom the placental separation probably did not influence the fatal outcome. Certainly in Case 1 (toxic series) the overwhelming *B. Welchii* infection was the major cause of death. This is a corrected maternal mortality of 9.2 per cent, occurring in the patients who developed moderate to severe placental separation.

However, even in the toxic group it is often the associated complications which occasionally develop but are resistant to treatment that account for the high maternal mortality. The corrected group (seven cases) contains two such

patients, successfully delivered, who died of bilateral cortical necrosis of the kidney. Another patient (Case 5, toxic series) died from shock and hemorrhage attributable to a defect in the blood-clotting mechanism. It is doubtful if any form of known treatment at the time would have altered the outcome in these cases. The four remaining deaths (Cases 4, 6, 7, and 8) constitute a mortality of 5.26 per cent within the toxic group, deaths accounted for by premature placental separation along with hemorrhage and shock. All four patients died undelivered. This suggests that some other form of treatment in these four cases might have improved the chances for recovery.

TABLE V. CRITERIA USED FOR CLASSIFYING DEGREES OF PLACENTAL SEPARATION

A. Mild.—	
	Pathological examination: ⅙ placental surface involved.
	No evidence of concealed hemorrhage.
	Less than 400 c.c. external bleeding.
	Labor progressing well.
B. Moderate.—	
	Pathological examination: moderate amount of retroplacental blood; over ⅙ but less than ⅔ of placenta involved.
	External bleeding over 400 c.c.
	Tense but not boardlike abdomen.
	Labor progressing well.
C. Severe.—	
	Pathological examination: Large amount of retroplacental blood; almost complete or complete involvement of placenta.
	Usually external bleeding of slight to moderate amount.
	Larger amount concealed hemorrhage.
	Uterus tense, tender, boardlike.
	Varying degrees of shock.

Treatment

The treatment instituted in cases of premature separation is commonly referred to as either the conservative or radical method. With the former the pregnancy is terminated vaginally while with the latter abdominal hysterotomy is the method of delivery. During the period covered by this study the method employed was in general the conservative type of treatment. This was particularly true of the patients who developed the severe toxic type of placental separation. A careful review of the maternal mortality in this entire series indicates that no one policy can apply to all cases of premature placental separation.

It will be noted that in patients with the nontoxic variety of placental separation and in cases of mild degrees of separation in the pre-eclamptic group, the risk to the mother was not greatly increased over normal pregnancy. Hence with this group one was concerned primarily with the welfare of the baby. In many of these cases, labor was in progress or at least uterine contractions were present when the patient was first observed. This was especially true in patients who subsequently proved to have vaginal bleeding due to either the rupture of a marginal sinus or a circumvallate placenta. One wonders in many of these cases whether the separation was produced by labor or whether the occurrence of the separation initiated the labor. In any event, examination to determine the diagnosis should be carried out with the proper facilities and precautions. Membranes should be artificially ruptured if this has not spontaneously occurred. This procedure is sufficient to improve the quality of the labor, decrease the possibility of further placental separation and arrest the bleeding. Delivery should be accomplished with low forceps as soon as is feasible after the first stage of labor has been completed, eliminating the risk of additional placental separation.

The use of cesarean section should be restricted to those patients who are not in labor and in whom vaginal examination reveals a cervix which is not effaced or dilated and in whom there is no evidence of fetal distress. It does not seem justifiable to submit the baby to an anticipated long labor under such circumstances with the risk of a stillbirth or neonatal death from intrauterine asphyxia.

Most of the controversy in this disease has been concerned with what constitutes the proper management of patients with severe degrees of placental separation, particularly when associated with hypertension and albuminuria. These cases contribute the major portion of the maternal mortality.

The treatment of severe placental separation by immediate hysterotomy followed by hysterectomy, should it be necessary to control further hemorrhage from an atonic uterus, has many advocates. This form of treatment has been predicated on the assumption that the myometrium, markedly infiltrated with blood, will not be able to function in a normal fashion during labor or following delivery. However many patients in the nontoxic group, the majority of the moderately toxic, and all of the severe toxic group in this series were treated by the conservative method. None of these patients died from postpartum hemorrhage due to uterine atony. It would appear that if hysterotomy has a place in the treatment of this condition, it must be concerned with problems associated with labor and delivery.

Analysis of the maternal deaths associated with moderate and severe separation revealed four patients who died undelivered (Cases 4, 6, 7, and 8) whose outcome might have been different if the conservative method had not been used. However, in this type of case the fetus is usually dead in utero when the patient is first observed and the purpose of emptying the uterus is concerned only with the welfare of the mother. Hence it is difficult to advocate immediate routine hysterotomy in these desperate cases, particularly if the patient is in shock when first observed.

TABLE VI. MATERNAL DEATHS CORRELATED WITH DEGREE OF TOXIC PLACENTAL SEPARATION 1931-1946

	TOTAL NO.	NO. MATERNAL DEATHS	PER CENT		CORRECTED FIGURES NO.	PER CENT	
Mild separation	124	0	0		0	0	
Moderate separation	58	6*	10.3	15.8	2	3.45	9.2
Severe separation	18	6†	33.3		5	27.7	

*Includes four patients with eclampsia.
†Includes one case with *B. welchii* infection.

There is one factor which is disturbing and has never been adequately investigated. This concerns an upset in the clotting mechanism of the circulating blood in certain cases of obstetrical hemorrhage.[21, 22] Whether this phenomenon is established by the time the patient comes under medical observation for her placental separation or develops during the course of the disease is an unanswered question.

Case 5 and the third death in the nontoxic group were quite similar in that both separated their placentas during the course of labor. Both had bleeding from other parts of the body at the time that the separation became a clinical entity. Blood studies performed in the latter case suggested the possible presence of a heparin-like substance as the etiological basis for the marked bleeding tendency. This evidence that alterations in the blood-clotting mechanism were present suggests that the change had already occurred by the time the separation

became evident. Moreover, it poses the interesting question whether or not the separation was the result of these changes in the coagulation of the blood rather than the cause.

Therefore, it seems reasonable that in patients who enter the hospital with evidence of shock associated with severe placental separation blood replacement should be given immediately. Rapid investigation of the clotting ability of the blood should be done and specific replacement, i.e., fibrinogen, vitamin K, etc., should be administered when indicated. During this time artificial rupture of the membranes should be performed. At the end of two to four hours after hospital admission and following replacement therapy, if no labor has ensued and the patient has fully recovered from shock, abdominal hysterotomy then appears to be the procedure of choice.

Certain substances released from the placental site[23, 24] might interfere with the blood-clotting mechanism.[22, 23] It might be argued that even the delay of a few hours in these severe cases is not warranted. However, immediate hysterotomy without adequate attention to the possible need for correcting any of these changes found in the blood might in reality result in an increase in the maternal mortality. Attention to the administration of the available specific corrective measures should lead to a lower maternal mortality in this most dangerous complication of the third trimester of pregnancy.

Summary and Conclusions

During the sixteen-year period from 1931 through 1945, 476 cases of premature separation of the normally implanted placenta occurred in 40,547 deliveries on the ward service of the Boston Lying-in Hospital, an incidence of 1 in 85 deliveries. Two classifications were devised for these cases with respect to etiology and the degree of clinical separation, respectively.

1. There were 276 nontoxic cases (58 per cent) of premature separation associated with 36,893 normal deliveries, an incidence of 1:133 deliveries.

2. There were 200 toxic cases (42 per cent) of premature separation in 3,654 cases in patients showing some degree of albuminuria and/or hypertension, an incidence of 1:18.3 Thus the increased frequency of premature separation with associated toxemia has been statistically established. Furthermore, the more severe the toxemia, the more frequent is the chance of premature placental separation.

3. A pathognomonic placental lesion common to all toxemic separations was not found. It is probable that acute atheromatosis of the decidual sinusoidal vessels is indicative of antecedent vascular or renal disease.

4. Old or recent placental infarction is present in a high proportion of toxic separation.

5. Fetal mortality, including stillbirths and neonatal deaths, was 34 per cent in the nontoxic group. Premature separation associated with toxemia increases the fetal loss nearly five times over that associated with toxemia alone. Premature placental separation tends to add a constant increment to fetal mortality, regardless of the degree of associated toxemia.

6. The maternal mortality for the entire series of placental separations was 3.1 per cent.

   a. In the nontoxic separations, the maternal mortality was 1.0 per cent.

   b. In the toxic separations, the maternal mortality was 6.0 per cent.

7. Maternal mortality in the toxic group is correlated with the amount of placental separation rather than the degree of toxemia per se.

8. The obstetrical management of these cases is discussed in the light of the maternal deaths reviewed.

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This instructive and informative essay may influence obstetricians to delay clamping of the umbilical cord, for these authors demonstrated that blood drawn from the superior sagittal sinus of ten infants whose umbilical cords were clamped immediately at birth presented mean values of 16.4 Gm. of hemoglobin per 100 c.c., 4,820,000 red corpuscles per c.mm., and 52 per cent hematocrit on the first day of life. These were contrasted with another series of ten infants, whose umbilical cords were not clamped until the placenta had separated from the uterus, who presented values of 20.6 Gm., 5,500,000 red corpuscles, and 60 per cent hematocrit.

Comparison of the blood picture in samples obtained by puncture of the sinus and puncture of the heel reveals that hemoglobin values and number of red blood corpuscles are significantly higher when the blood was obtained from the peripheral capillaries.

They also call attention to the continuation of a state of activity of the erythropoietic system, leading to maintenance of a higher reticulocyte percentage in the group of infants whose cords were clamped at the moment of birth. This we presume to be evidence that the infant is compensating for having been deprived of his full complement of blood by the hasty clamping of the umbilical cord. JAMES P. MARR.

ELECTRICAL ACTIVITY OF THE HUMAN UTERUS IN LABOR*
The Electrohysterograph

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ATTEMPTS to record the electrical activity associated with contraction of the human uterus in labor have been described by Bode,[1] by Clason,[2] and by Dill and Maiden.[3, 4] In 1931 Bode applied metal electrodes to the abdomen of a patient in labor and made a record with the string galvanometer. His record shows an irregular deflection of the string with a contraction, the deflection becoming less as the uterus relaxed. This type of deflection represents a slow change in DC potential, with some faster diphasic activity superimposed. No mechanical recording was made, so that the exact relation of the electrical activity to the uterine contraction is unknown. In 1934, Clason applied electrodes to the abdomen and thigh of a patient in labor and recorded with a string galvanometer. His record is similar to that of Bode. In 1946, Dill and Maiden reported a study of eighteen patients in labor, using two types of apparatus, one suitable for recording slow changes in DC potential, the other suitable for recording rapid AC changes. They concluded that "contraction of the uterine muscle during labor in the human is accompanied by changes in potential of low frequency and voltage." In 1948, Dill and Maiden described a further study, in which simultaneous recordings were made from three points on the abdominal wall, using a direct-coupled electrical system capable of responding to very slow changes of potential. They reported that early labor was associated with electrical activity at one point; as labor advanced two points became active; and when strong labor was present all three points produced the same record. They did not describe the variation of their records from pain to pain or patient to patient.

The electrical activity of uterine muscle in laboratory animals has been more extensively studied. Bozler[5-10] and Balassa[15] have examined uterine muscle strips and the action potential has been recorded. The exposed or isolated uterus of the cat, rabbit, and guinea pig has been examined by Morison,[17] Balassa,[16] and others,[12-14, 18-21] and it has been demonstrated that the contracting uterus produces characteristic electrical activity which varies with the presence of estrogens or progesterone, and with various stages of pregnancy. The records of Morison with the cat uterus in estrus, obtained by placing electrodes directly upon the exposed uterus, are remarkably similar to the records obtained in this study from the human uterus.

*Read before the New York Obstetrical Society, Jan. 11, 1949.

The study reported in this paper was begun on this background, with the exception of the second paper of Dill and Maiden. The study was therefore made from an exploratory standpoint, in order to determine what electrical activity existed, what its characteristics were, where it might best be found, and how it might best be recorded. For these purposes several different systems of electrical apparatus were constructed.

Apparatus: The Electrohysterograph

There has been developed an apparatus which may be called the Electrohysterograph (or EHG). This allows recording on six channels simultaneously, the writing being done by electrically activated pens on chemically sensitive paper. The six channels furnish adequate space for a simultaneous electrical, mechanical, and subjective study of the patient in labor.

A diagram of this apparatus is shown in Fig. 1. The first three channels record the electrical potential. These channels consist of vacuum tube differential amplifiers, resistance capacity coupled, which are connected with three pairs of electrodes on the patient's abdomen (or elsewhere as desired). The fourth and fifth channels are connected with strain gages located on the abdominal wall over the upper and middle portions of the uterus, and are operated by carrier type amplifiers. The sixth channel is connected with a hand switch by means of which the patient can signal the beginning and end of each "pain."

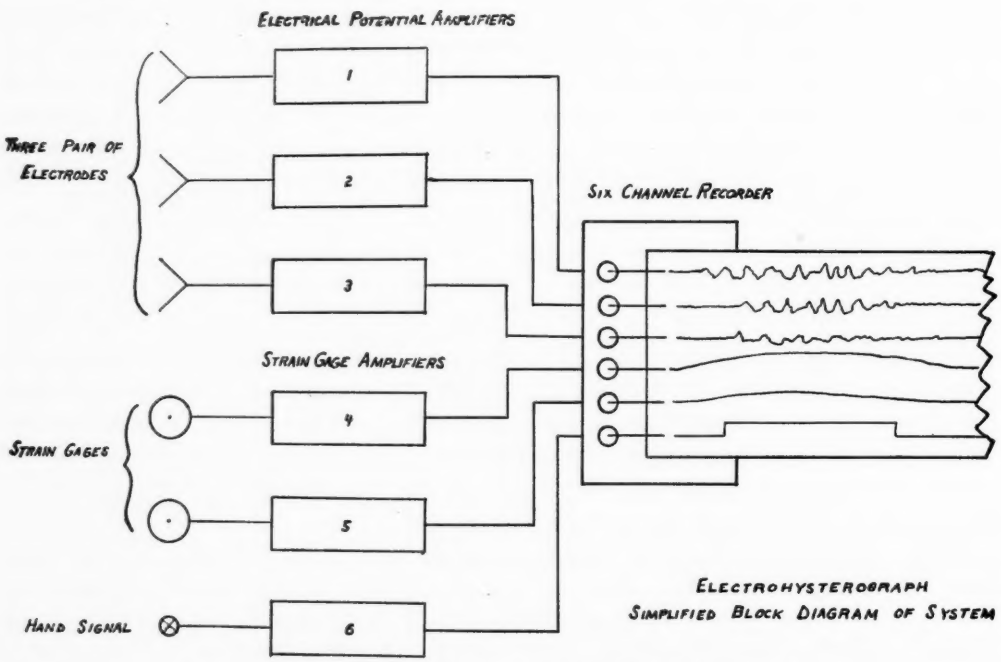

Fig. 1.—Block diagram of six-channel Electrohysterograph.

This apparatus (which is an AC system) is the final result of extensive exploration and modification. In addition, studies have been made with one other type of AC system and two types of DC systems:

1. A pre-amplifier (modified Toennies circuit) plus cathode-ray oscilloscope, feeding a magnetically driven pen-writer.

2. A push-pull direct-coupled amplifier driving an Esterline-Angus recorder.
3. A direct-coupled amplifier driving the oscilloscope, recording by a slow 35 mm. camera.

These systems have the following characteristics:

SYSTEM	SENSITIVITY	REJECTION RATIO (AT 60 CPS*)	FREQUENCY RESPONSE (BAND WIDTH)
1. Pre-amplifier plus Oscilloscope plus Pen-writer	.135 mm./microvolt (screen) .067 mm./microvolt (pen-writer)	50×10^3	1-18,000 cps (scope) 1-40 cps (pen-writer)
2. DC amplifier plus Esterline-Angus Recorder	10 mm./millivolt	1×10^3	0.8 cps
3. DC amplifier plus Oscilloscope plus Camera	25 mm./millivolt	4×10^3	0-8000 cps
4. Electrohysterograph (EHG)	.067 mm./microvolt	5×10^3	.11-30 cps or .22-30 cps

*Cycles per second.

In order to obtain an accurate representation of the input wave, it is necessary that the recording system satisfy the following requirements:

1. The system should respond uniformly through a range from direct current to a frequency at least ten times the highest frequency component being measured.
2. The deflection of the recording element should be proportional to the potential of the input wave.
3. The input impedance of the amplifier should be high (one megohm or greater).
4. The inherent noise level must be less than the minimum signal to be recorded.
5. Drift must be kept to a minimum.
6. A good transient response must be obtained.
7. In addition, a differential amplifier is preferable to a single-grid input system, to cancel in-phase pick-up.

However, this ideal arrangement must be modified by certain practical considerations, notably the presence of the standing potential and other potentials which vary extremely slowly, response to which is not desirable. When an apparatus is constructed which meets these practical considerations, the response to very low frequencies is less than in an ideal system, the distortion introduced being dependent upon the low frequency characteristics of the amplifier. The apparatus described herein has been found satisfactory for our purposes, and systems with similar characteristics will be satisfactory for clinical investigations. For study of action potentials, and other biopotentials, apparatus meeting the ideal requirements will be necessary.

Electrodes

For the AC systems, including the EHG, solder pellets 2 mm. in diameter are used. These are applied over electrode jelly and held in place by a small piece of adhesive tape. They are connected to the amplifiers by very flexible wire.

The electrodes are usually placed on the abdominal wall in pairs about 6 cm. apart. For routine purposes the outlines of the uterus are palpated, and one pair of electrodes is placed as close as possible to the left uterine cornu; a second pair is placed similarly at the right cornu; and the third pair

is placed high in the midline of the fundus. For exploratory purposes these electrodes have also been placed on the lower half of the abdomen and on all extremities. The ground electrode is attached to the left or right flank.

For the DC systems, wet electrodes of the silver-silver chloride-normal saline type are used. On the abdomen, these consist of glass tubes with an internal diameter of 5 mm., closed with a cotton plug, and mounted in rubber stoppers. These are held in place with adhesive tape and double-coated Scotch tape. On the extremities, paper cups filled with saline are used.

In addition, chlorided silver wires have been used directly in the exposed uterus and in the excised uterus, and stainless steel wires have been used in the cervix and in the excised uterus.

Material

The patients studied were all taken from the labor rooms of the Sloane Hospital for Women. They were in varying stages of labor, and, since the characteristics of normal labor were investigated first, the largest number of patients is in the group with clinically normal labor. The clinical impression in each case was confirmed by checking on the final outcome of labor.

A total of 78 patients have been studied. Of these, 69 were examples of normal labor; 8 exhibited uterine inertia; and 1 was in false labor. In addition, 6 of the patients in normal labor were studied earlier, when false labor was present, so that 7 instances of false labor were recorded.

In all, 114 tests were performed on these 78 patients, 70 with an AC system; 23 with a DC system; and 21 with the strain gages. Many of these were performed before the final Electrohysterograph was developed, but 20 patients have been studied with this very complete device. One test was made at cesarean section, by inserting chlorided silver wires directly into the uterus; and an additional test was made on a uterus excised at the time of cesarean section.

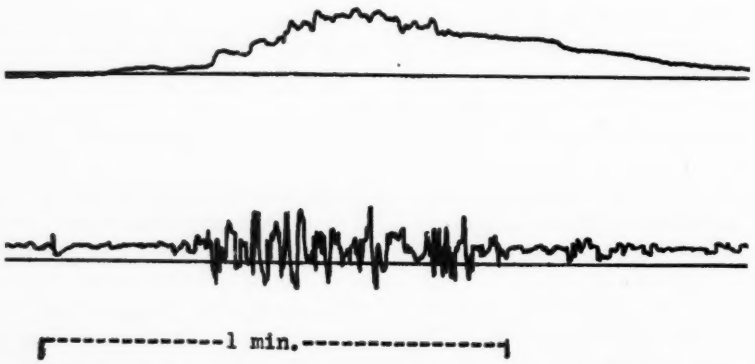

Fig. 2.—Slow speed recording showing relation of mechanical and electrical (AC) activity. A, Mechanogram. B, Electrical record. One pair of electrodes on abdomen. Time intervals 1 minute. Calibration 120 microvolts.

Results: The Origin and Characteristics of the Observed Electrical Activity

Normal Labor: AC Systems: Electrodes on Abdominal Wall.—

During normal labor, the Electrohysterograph (AC system) shows a characteristic sequence of activity. Between contractions there is seen a relatively smooth tracing, on which the electrocardiogram may be recorded if the leads are placed high on the abdomen. Beginning with the onset of a contraction, there appear irregular waves which sometimes appear almost

sinusoidal. These have a frequency of 1/3 cps to 2 cps, and an amplitude varying roughly between 100 and 500 microvolts. The amount of activity varies from patient to patient, but during normal labor it is always seen. This activity, with its relation to the mechanical activity, is demonstrated in Fig. 2, a slow speed recording.

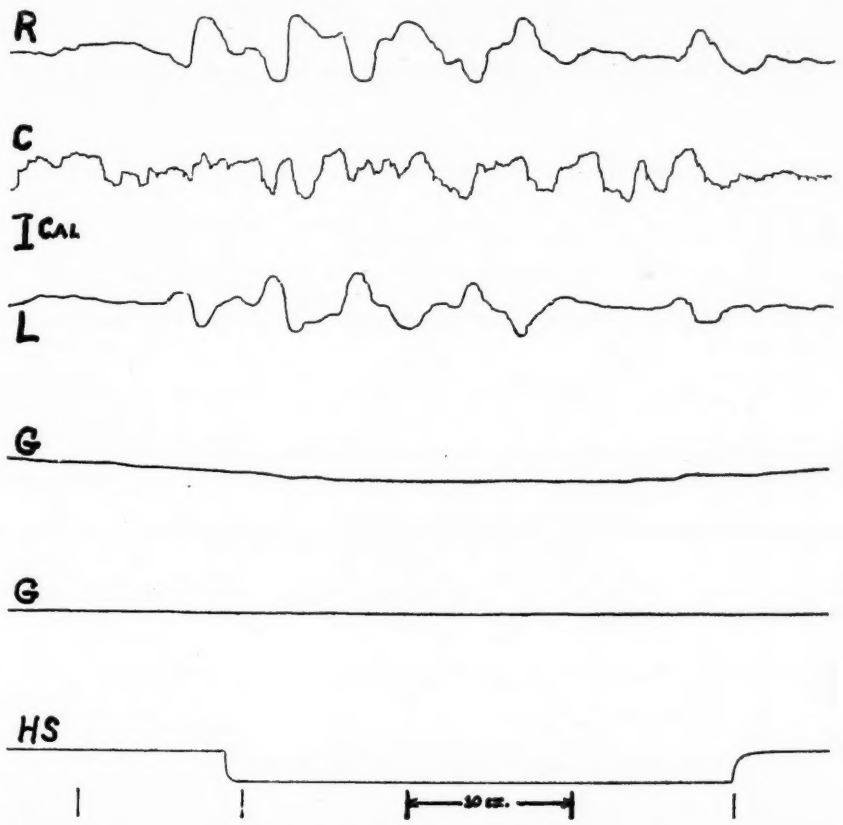

Fig. 3.—Six-channel record of normal labor using the Electrohysterograph. Electrodes on abdominal wall. Channels from above downward: R, electrodes near right cornu; C, electrodes in midline of fundus; L, electrodes near left cornu; G, strain gage on fundus; G, strain gage on lower half of uterus; HS, hand signal on which patient signals the presence of pain.

When all six channels of the Electrohysterograph are used, the sequence of electrical, mechanical, and subjective events is readily demonstrated (Fig. 3). The electrical activity begins simultaneously with movement of the strain gage. Some ten to twenty seconds later, the patient begins to feel pain. The pain persists until the electrical activity stops, at which point the uterus is beginning to relax, as indicated by the strain gage. Relaxation takes twenty to sixty seconds more, during which time no further electrical activity is seen. The gage record slowly returns to the base line, and no further change occurs until the onset of the next contraction.

The correlation of uterine activity with the electrical record is well shown in Figs. 4 and 5. This patient had been in very early labor and was sedated too soon. She went into rather a deep sleep, all contractions ceased, and she was followed electrically for forty-five minutes with no evidence of activity.

She was then given one minim of Pitocin intramuscularly. A sample of the record at that time is shown in Fig. 4, *A*. Eight minutes later the activity seen in Fig. 4, *B* was recorded, and the uterus was seen to contract. The patient continued to sleep. Contractions then occurred about every three minutes. Eleven minutes after the injection the patient stirred with the contraction, and, when questioned, said she had slight pain (Fig. 5, *A*). The contractions increased in strength thereafter, until at twenty-one minutes after the injection (Fig. 5, *B*) the pain was so strong that she moved about, the rapid activity seen in this record being produced by the voluntary muscles.

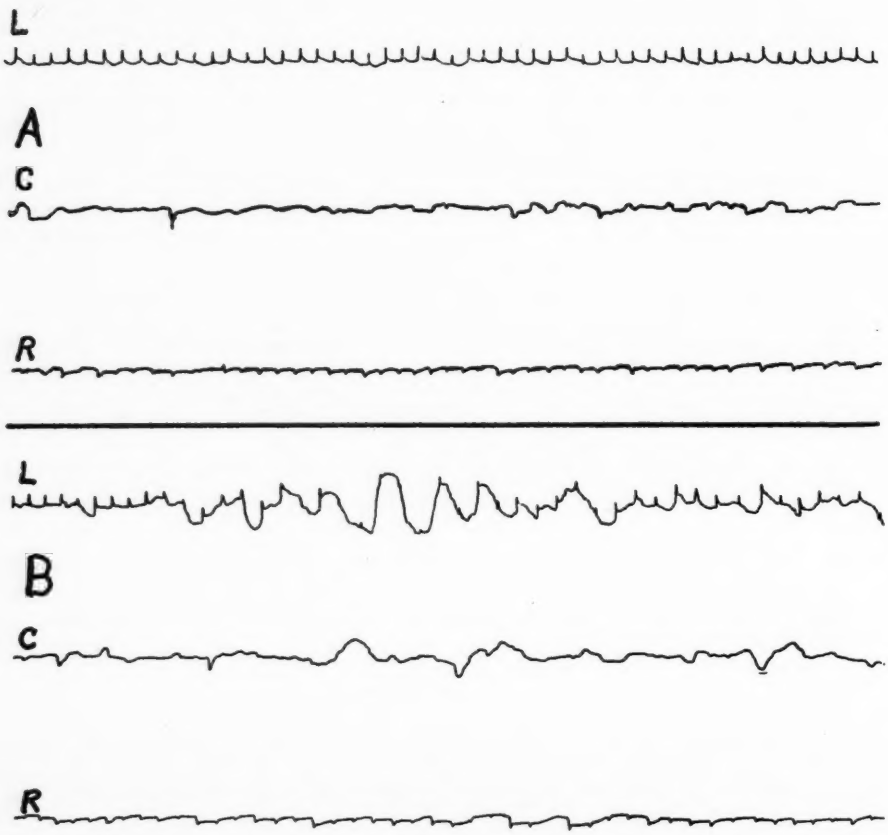

Fig. 4.—Three-channel recording of induction of labor. Electrodes on abdominal wall. Channels from above downward: L, electrodes near left cornu; C, electrodes in midline of fundus; R, electrodes near right cornu. Legend the same for Figs. 4 and 5. Calibration and time interval as shown in Fig. 5, B. Calibration 150 microvolts. Time interval 10 seconds. A, Before labor. B, Eight minutes after injection of 1 minim of Pitocin intramuscularly.

This record also shows an interesting sequence of electrical changes. In Fig. 4, *B*, with the earliest contraction, the left lead shows the earliest and the greatest activity, the center lead showing very little and the right none. In Fig. 5, *A*, the left lead again shows activity first, with the center lead next, and the right lead last. In Fig. 5, *B*, all three leads are active, with the center lead first by a small time margin.

This type of record, which suggests the phenomenon of propagation, is seen in early labor. Usually the left lead is first, but this is not always so. When strong labor is present, on the other hand, all three leads show activity, and all three seem to begin simultaneously.

It becomes apparent, then, that uterine contraction during normal labor is accompanied by AC changes which may be seen in one or two leads in early labor but which are present in all three leads when good labor is established.

This activity is picked up routinely from the surface of the abdomen, with one pair of leads near each uterine cornu and the third pair on the fundus. Practically no activity is found with paired electrodes on the lower abdomen.

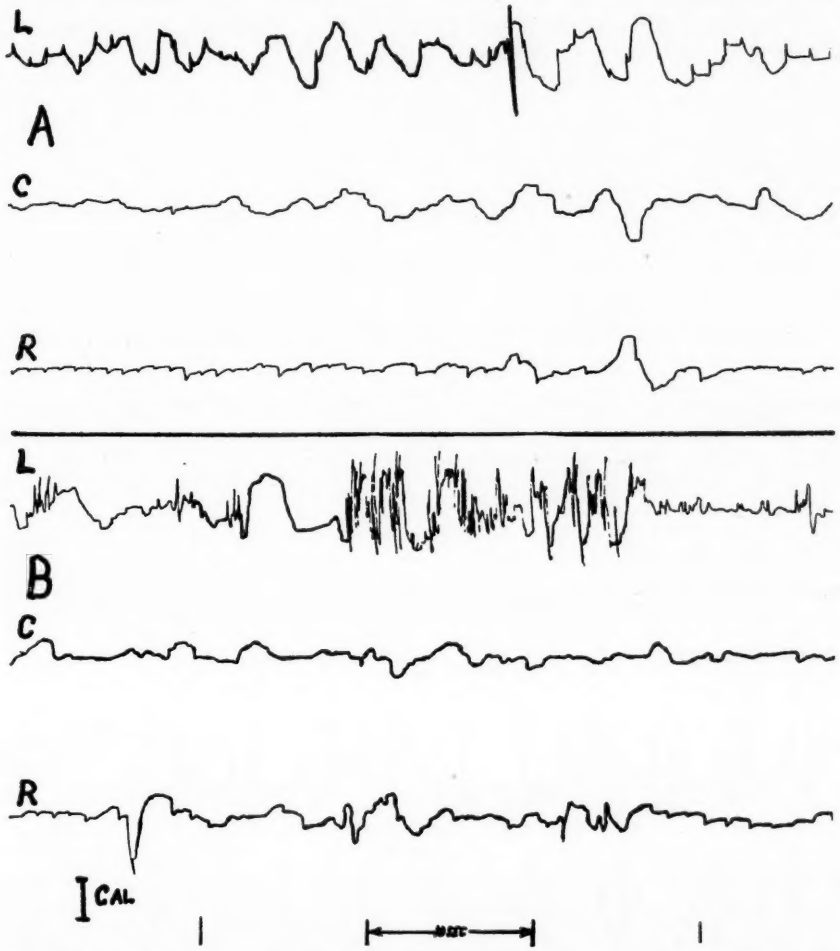

Fig. 5.—Same case as Fig. 4. A, Eleven minutes after Pitocin. B, Twenty-one minutes after Pitocin. Note the rapid spikes in the upper tracing, produced by voluntary muscle activity.

Normal Labor: Electrodes in Cervix and on Extremities.—

Leads have also been placed in the substance of the cervix (stainless steel wires 2 mm. apart). These leads show activity similar to that found on the abdomen, except that the waves are of lower amplitude and somewhat greater frequency (Fig. 6, *C*). When the extremities are used, large, slow waves with the electrocardiogram superimposed are recorded (Fig. 6, *E*). When one lead is placed in the vagina and the other on the leg, a record similar to Fig. 6, *C* is also obtained.

The Excised Puerperal Uterus.—

These findings suggest that the electrical activity associated with uterine contraction originates in the uterus. This impression is strengthened by the

similarity of the record to that obtained by Morison from the exposed estrus cat uterus. An excised puerperal uterus, obtained at cesarean section, was next examined. Stainless steel wires were placed in the uterine wall at a distance of 3 cm. When the recording was begun, three hours after removal, the uterus was found to be giving off slow waves similar to those obtained from the abdominal leads during labor (Fig. 7, *A*). These waves were of complex form, at a frequency of ¼ to ½ cps, and occurred in bursts of five to seven waves. Between bursts were slow, more or less constant waves lasting about three minutes.

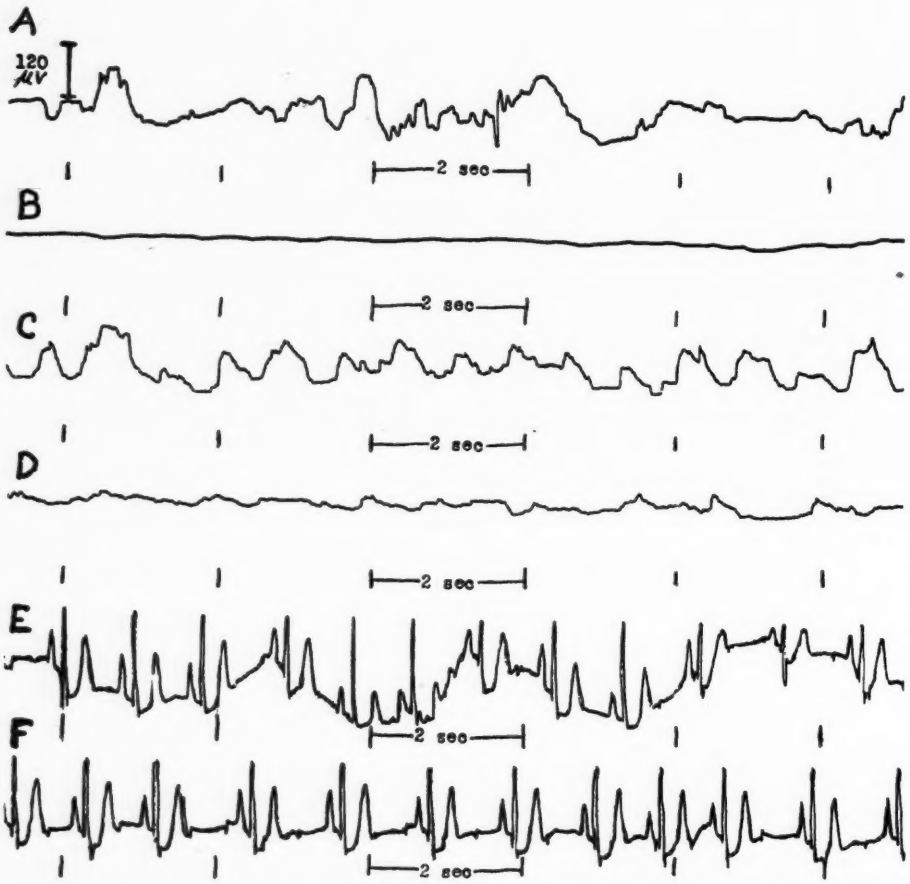

Fig. 6.—Electrical activity from three different parts of the body. A and B, Electrodes on abdominal wall. C and D, Electrodes in the anterior lip of the cervix. E and F, One electrode on right arm and one on left foot. (Note large EKG in E and F.) A, C, and E, Samples taken *during* a contraction. B, D, and F, Samples taken *between* contractions. Time intervals, 2 seconds. Calibration, 120 microvolts.

This activity persisted for two and one-half hours, gradually becoming less frequent. Mechanical stimulation (with a pair of forceps) gave one or two waves. Electrical stimulation gave two or three waves.

At five and one-half hours after removal, Pitocin was injected between two electrodes placed 3 cm. apart. This injection was given in doses of 3 minims at five different spots. There was always an immediate reaction in the record which was almost certainly mechanical. Within a few minutes increasing activity of the type usually seen with electrodes on the abdomen began again.

This increased in frequency, amplitude, and duration, until at a time forty minutes after the first injection of Pitocin, and twenty minutes after the last, there was intensive activity (Fig. 7, *C*) which is indistinguishable from the activity obtained with abdominal leads. This marked activity continued for thirty minutes and then gradually diminished. At eight hours after removal almost no activity remained.

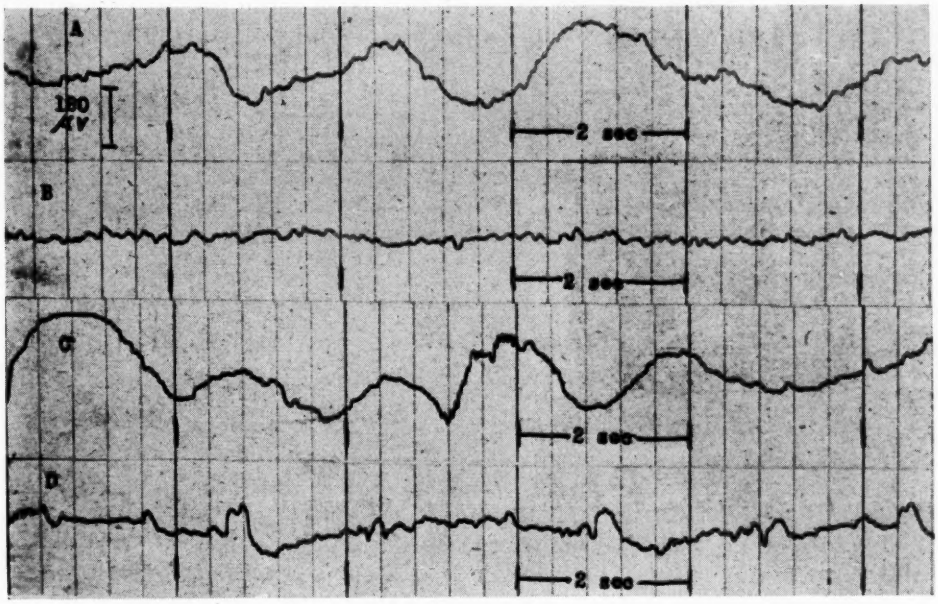

Fig. 7.—Electrical activity of the excised puerperal uterus. AC system. Wire electrodes 3 cm. apart in the uterine muscle. A, Spontaneous activity. B, Quiet period. C, After Pitocin. D, Quiet period. (See text.) Time intervals, 2 seconds. Calibration, 120 microvolts.

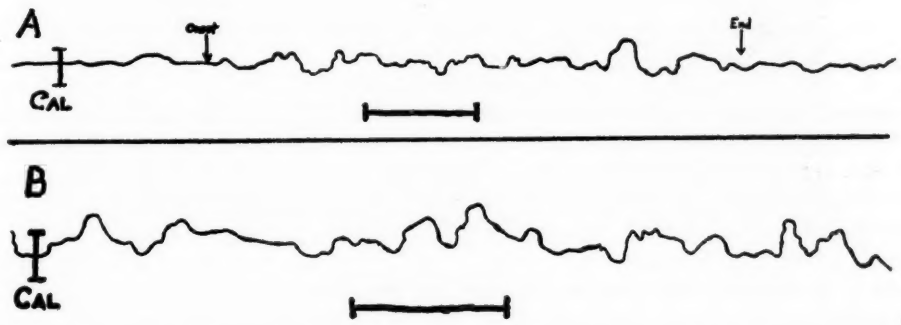

Fig. 8.—Electrical activity of the exposed uterus in labor at cesarean section. AC system. Time interval, 10 seconds. Calibration, 300 microvolts. Electrodes in uterine wall. A, Electrodes 3 cm. apart. Entire duration of one contraction shown. B, Electrodes 6 cm. apart. A longer contraction than in A, onset and end not shown.

Normal Labor: Electrodes in the Exposed Uterus.—

The uterus was finally proved to be the origin of the recorded waves by examining the exposed uterus at cesarean section. The patient, a young primipara, had been in labor for eight hours, and x-ray pelvimetry revealed absolute disproportion. The operation was performed under continuous spinal

anesthesia, the pains at the time of operation occurring every five minutes. The junction of the middle and lower thirds of the uterus was exposed, and chlorided silver wires were inserted into the wall for a distance of 2 mm. Recordings were made with the electrodes at distances of 3 cm. (Fig. 8, *A*) and 6 cm. (Fig. 8, *B*). The ground electrode was also placed in the uterine wall. It was not possible to use a mechanogram under these circumstances, but the uterus was observed to contract regularly.

The records reveal the presence of the same irregular waves, at a frequency of 1/3 cps, which are found on the abdominal wall during normal labor.

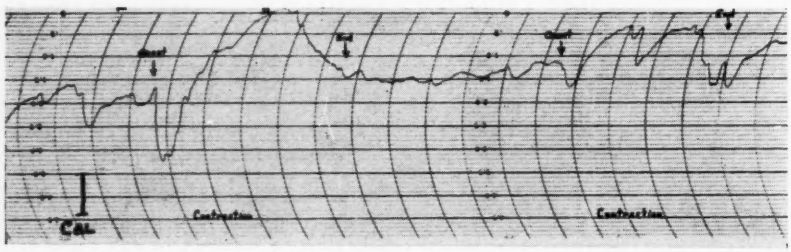

Fig. 9.—Slow speed DC record. Normal labor. Electrodes on abdomen. Calibration 1 millivolt. Time interval (curved transverse lines) 15 seconds. Two consecutive contractions shown.

Normal Labor: DC System.—

A total of twenty-three cases of normal labor were studied with the DC systems. Each contraction is found to be associated with a slow, irregular, and variable wave. When the electrodes are first applied, a "standard potential" is always found varying from 5 to 25 or more millivolts. The waves associated with uterine contraction are superimposed on this potential. The wave appears to begin after the contraction has started. It may be monophasic or diphasic, but it continues long after the contraction is completed. There is almost never a return (amplifier drift being taken into consideration) to the potential which existed before the onset of the contraction.

Two such waves are shown in Fig. 9. This patient was in normal labor. The contractions were all equal in duration and strength, as far as could be determined clinically. Nevertheless, the DC waves were all different, and no consistent pattern was found. Some faster waves are also seen superimposed on the large slow waves. These faster waves, at a frequency of 1/3 to 2 cps, are the waves seen in the AC records. These waves are modified in this type of record because of different characteristics (amplification and speed of response) of the system.

It is evident, then, that a contraction of the human uterus during normal labor is accompanied by a very slow DC change, which is highly variable in the same patient, and also by a more rapid change best shown by AC systems, which is characteristic and reproducible from pain to pain and from patient to patient. The co-existence of these two phenomena is demonstrated by the use of system No. 3, a direct coupled amplifier driving a cathode-ray oscilloscope, the recording being made by a 35 mm. camera with a film speed of 25 cm. per minute. This record (Fig. 10) shows a total shift of the base line during a contraction of about 2.5 millivolts. Superimposed on this are waves at a frequency about 1/3 cps and amplitudes of 100 to 300 microvolts. It may be noted that this system is capable of recording activity as rapid as 8,000 cycles per second with greater camera speed, but no waves faster than 2 cps. are found.

Results: The Electrical Pattern of Labor

This investigation has demonstrated that the contracting human uterus produces electrical activity which may be picked up by electrodes placed on various parts of the body. For practical purposes, the abdominal wall is the best site for placement of the electrodes. In the first place, it is easy and convenient to place electrodes on the abdominal wall, and there is no question of contamination of the reproductive tract. More important, however, placing of electrodes on the abdominal wall, close to each uterine cornu and to the midline of the fundus, allows the recording of different patterns of activity at various stages of labor and during abnormal labor. For these purposes three points must be studied during each contraction.

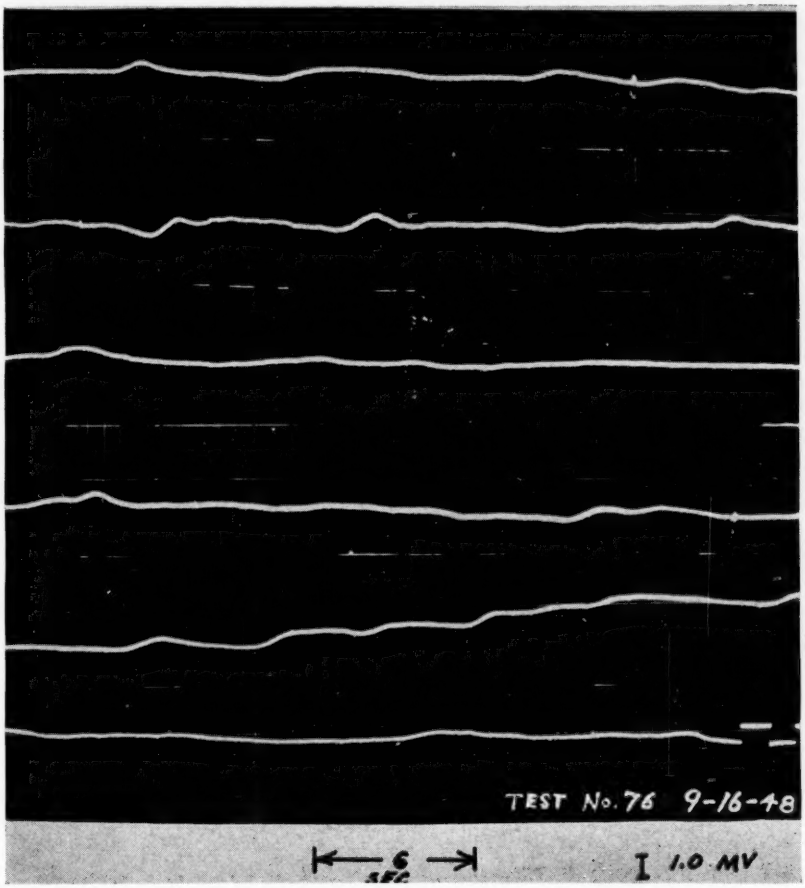

Fig. 10.—Record of normal labor with DC system (oscilloscope and 35 mm. camera). Time interval, 6 seconds. Calibration, 1 millivolt. Contraction begins at top left and ends at bottom left. Note slow shift of base line with small waves superimposed.

Normal Labor (69 Cases).—

The pattern of normal labor is shown in Fig. 3. There are two significant features. First, the electrical activity consists of characteristic waves at a frequency of about 1/3 cycle per second and an amplitude of 100 to 500 microvolts. When these are present, normal labor *is present or impending.* Second, the electrical activity may be found in one, two, or all three of the leads. In well-established, active labor, activity is seen in all three leads, and the activity is qualitatively much alike in all three leads.

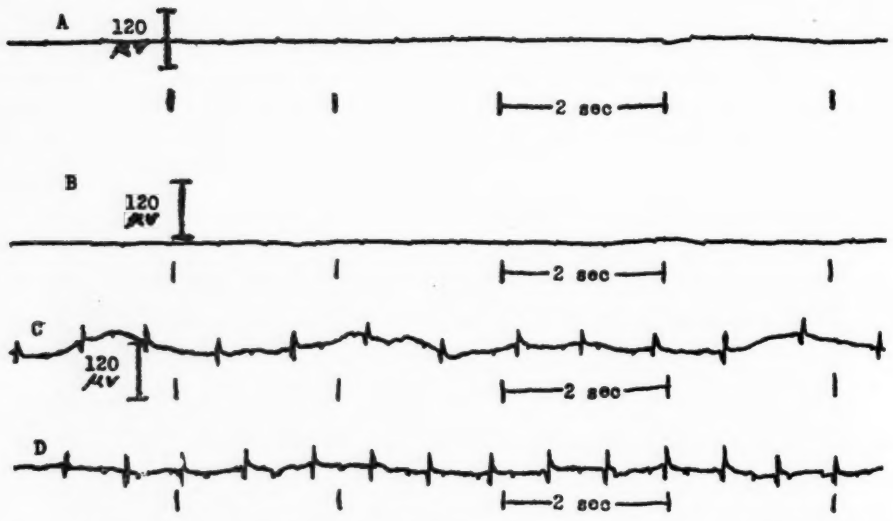

Fig. 11.—Uterine inertia. Two cases. AC system, one pair of electrodes on abdomen. A and C, During a contraction. B and D, Between contractions. Time intervals, 2 seconds. Calibration, 120 microvolts. Larger electrocardiogram waves in C and D due to placement of electrodes nearer heart.

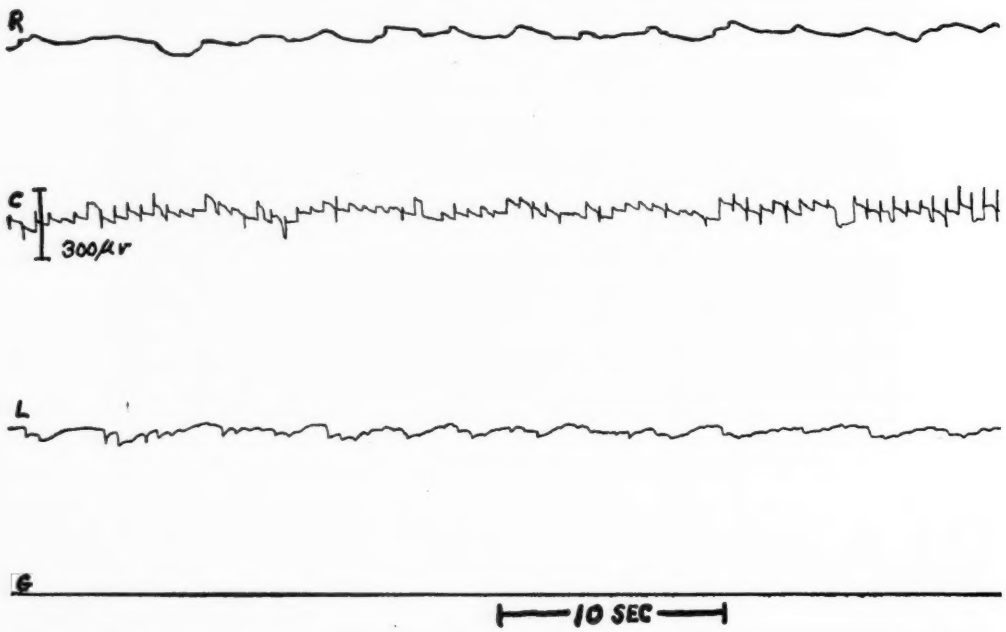

Fig. 12.—Uterine inertia, between contractions. (See text.) Electrohysterograph. In Figs. 12, 13, and 14: Time intervals, 10 seconds. Calibration, 300 microvolts. Channels from above downward: R, electrodes near right cornu; C, electrodes in midline on fundus; L, electrodes near left cornu; G, strain gage on fundus.

Early Labor (19 Cases).—

In early labor, electrical activity of the characteristic type is seen in one or two but not in all three leads, as shown in Figs. 4, *B* and 5, *A*. The frequency remains about 1/3 cps, but the amplitude is usually smaller than in strong, active labor. The total duration of the activity is relatively short. As labor progresses, the activity becomes longer in time; the amplitude of the waves increases, and one, then two, then all three leads show the activity.

There is also seen, in early labor, phenomenon strongly suggestive of propagation of an impulse. This is well shown in Fig. 5, *A*. The activity begins in the left lead, is then seen in the center (or fundus) lead, and is seen last in the right lead. As labor progresses, the interval between activity in one lead and in the next becomes shorter, until all three leads begin to show activity at the same time.

The point at which activity is first seen may be any one of the three: right cornu, left cornu, or fundus, as records from different patients are compared. In the same patient the same point usually but not always leads.

False Labor (7 Cases).—

In false labor activity is seen in one or two leads only, as shown in Fig. 4, *B*. This type of record is indistinguishable from that of very early normal labor. The frequency is 1/3 to 1 cps, and the amplitude is usually 100 to 300 microvolts. When "true" labor subsequently begins, there is extension of the activity from the one lead to all three.

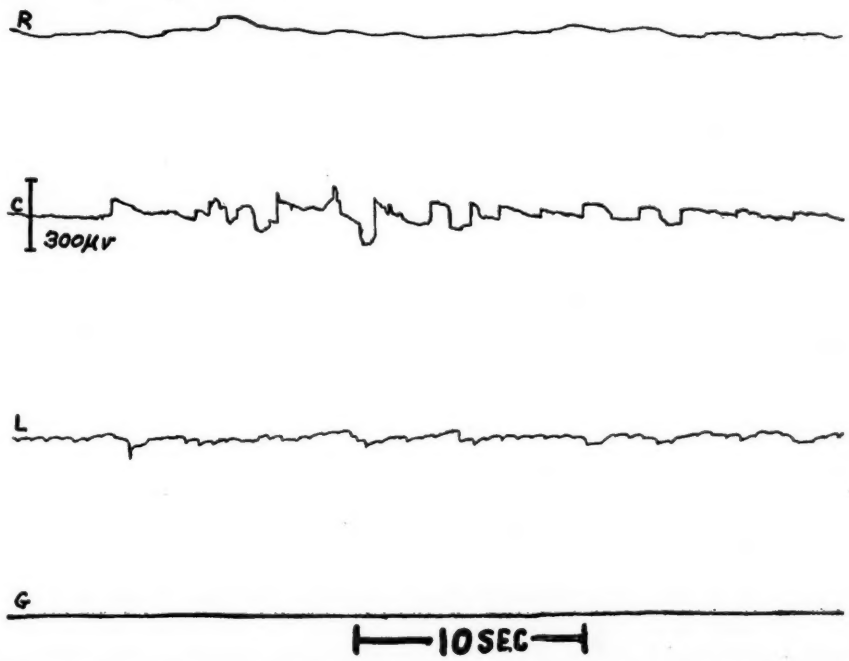

Fig. 13.—Uterine inertia during a spontaneous contraction. Same as in Fig. 12.

Uterine Inertia (8 Cases).—

The pattern of labor in uterine inertia is shown in Figs. 11 to 14. When only one lead was used (7 cases) no electrical activity was found, although various points on the abdominal wall were tested in each patient. When three simultaneous leads were used (1 case) the record shown in Figs. 12, 13, and 14 was obtained. There are two features by which this record varies from that of normal labor:

1. Activity is seen in but one lead (Fig. 13).

2. The electrical activity is very irregular, with sharp waves superimposed, and the over-all pattern does not resemble that of normal labor.

This patient had been in labor for forty hours, with pains which were strong for a time, and then weak. The cervix had reached 3 fingers' dilatation. The patient had been rested with morphine and an infusion twelve hours before the test. After the record of Figs. 12 and 13 had been obtained, an infusion of 1 c.c. of Pitocin in 1,000 c.c. of 5 per cent dextrose was begun. The pains became stronger, and at one point, with the infusion running at 45 drops per minute, she had a continuous contraction lasting about two and one-half minutes. The record in Fig. 14 was obtained at that time.

This record shows activity in *two* leads, but none at all in the third. The activity in the two leads is *not* that of normal labor, but consists in irregular waves (many of them with a superimposed spike pattern due to voluntary motion) at a frequency nearer 1/5 cps than the usual 1/3 cps.

This patient never developed good labor. The Pitocin was discontinued; she was given morphine, and the delivery was completed by midforceps and manual dilatation of the cervix eighteen hours after the above record.

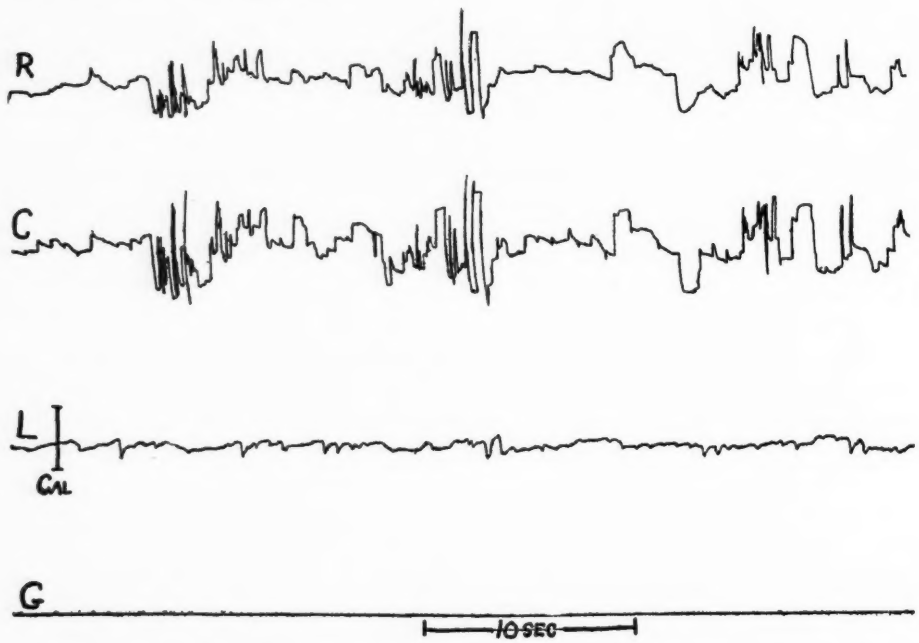

Fig. 14.—Uterine inertia during a long contraction induced by Pitocin infusion. Same as Figs. 12 and 13. Note sharp waves and voluntary muscle activity.

It must be noted that the number of cases of uterine inertia studied is too small to warrant final conclusions. The records in all eight cases, nevertheless, have been greatly different from the records of normal labor, and it seems possible that further studies will prove this to be a useful method of differentiating normal from abnormal labor.

Discussion

It has been demonstrated that the human uterus, contracting during labor, produces electrical activity which can be recorded from the abdominal wall or from other parts of the body. This electrical activity consists of a

characteristic and reproducible series of complex waves, with frequencies of 1/3 to 2 cycles per second and amplitudes of 100 to 500 microvolts. At the same time, there is an associated change in the standing potential consisting of a very slow wave of irregular form, not reproduced from pain to pain in the same patient, with peaks of 1 to 5 millivolts.

This study has demonstrated that early labor is associated with electrical activity at one of three usual points on the abdominal wall (close to each uterine cornu and to the midline of the fundus). As labor advances, two leads become active, and in strong labor all three leads show essentially the same activity. Evidence has also been found which suggests the phenomenon of propagation of electrical activity during early normal labor.

These findings are in agreement with those of Dill and Maiden, who have also found, by studying the very slow waves with a DC system, that electrical activity begins in one lead during early labor, then appears in two, and finally is seen in essentially the same pattern in all three leads when strong labor is established.

There has been demonstrated a different type of electrical record in uterine inertia. In this condition electrical activity either is absent or, if present in one lead, is of a slow and irregular frequency with sharp waves superimposed. Most of the sharp waves are due to voluntary motion.

These patterns of electrical activity suggest a theory of the action of uterine muscle during labor. Considering the muscular portion of the uterus as a unit, it appears that muscular activity begins at one point in early labor and then spreads to the remaining muscle as labor advances. In early labor, with activity at one point leading the activity at the next point by as much as ten seconds, it is possible to assume that the original point acts as a pacemaker. In strong labor, when all three points begin simultaneously and show similar electrical patterns, it seems that activity begins at the same time at several points. The alternative to this is to assume extremely rapid transmission of the original impulse from the pacemaker. There is no evidence to point to any one particular portion of the uterus as the pacemaker, since the earliest activity has been found at both cornu and on the fundus, when various patients are compared. There is practically no activity seen in the lower portion of the uterus (which agrees with the mechanical findings of Reynolds).

It can be demonstrated histologically that the uterine muscle fibers are joined together by fine protoplasmic continuations which vary in size. Bozler has shown that small pieces of uterine muscle behave as a unit, that is, they react electrically as a true functional syncytium. The reactivity of this muscle depends upon the presence of estrogens (among other substances), and variation of reactivity depends upon transmission of the electrical impulse over large or small numbers of these fibers. When reactivity is slight, there is little transmission, and consequently only a small number of fibers will contract *as a unit.*

The action potential of uterine muscle fibers is a monophasic spike of short duration. The waves recorded from the abdominal wall or directly from the exposed uterus are complex and irregular. It is possible to explain these complex waves as the result of contraction of a large group of fibers, the form of the wave being distorted by the activity of adjacent groups of fibers and by transmission of the waves through a mass of tissue. In normal labor, then, there are large groups of fibers reacting as large syncytia more or less simultaneously. This produces a strong contraction of a large segment of the uterine muscle, and when this process goes on in all the adjacent syncytia within a short time the efficient contraction of normal labor results.

In uterine inertia this type of activity is not seen. There is often no appreciable electrical activity on the surface of the abdomen, despite a hard, painful contraction. When activity *is* seen, in one lead, the waves are short, sharp, and irregular. This type of record suggests that only very small groups of fibers are contracting as a unit, and that the electrical output of most of these units is too small to reach the surface. The individual fibers contract to some extent in this condition, producing hardening and pain, but because of lack of transmission of the electrical impulse no effective mechanical activity is produced. The basic defect in uterine inertia is thus a lack of "excitability" of the individual fibers and their protoplasmic extension.

These conclusions are based on a relatively small number of cases, but the findings in each group of cases are consistent. Further work is in progress, with particular attention to uterine inertia. It is hoped that the rather striking difference between the patterns of normal labor and uterine inertia will be found valid, so that an objective method of diagnosing uterine inertia may be established. On the basis of the tests described, it seems that AC coupled systems are superior for this purpose, since they yield records which are reproducible and comparable from one patient to another.

Summary

1. Methods of recording the electrical potentials produced by the human uterus in labor are described.

2. The characteristics of this electrical activity are illustrated.

3. The uterus is proved to be the site of origin of this electrical activity.

4. Patterns of false labor, early labor, advanced labor, and uterine inertia are described.

5. The relation of electrical activity to uterine action is discussed.

6. The possibility of differentiating normal from abnormal labor by this means is proposed.

The authors wish to express their gratitude to Dr. Howard C. Taylor, Jr., who made this study possible; to Dr. S. R. M. Reynolds and Dr. H. Grundfest for valuable suggestions; to Dr. P. F. A. Hoefer and Mr. C. J. Markey for the use of certain apparatus; and to the nursing staff of the Labor Room of the Sloane Hospital for Women for their kind cooperation.

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INTRAVENOUS PITUITARY EXTRACT IN LABOR WITH DATA ON PATTERNS OF UTERINE CONTRACTILITY*

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SEVERAL recent papers have pointed to the safety and efficacy of small doses of pituitary extract in the treatment of uterine inertia.[3, 6] In a survey of much the same data that was presented by Eastman, one of us[4] pointed out that the failure rate in the treatment of delayed labor with intermittent intramuscular pituitary extract was in the neighborhood of 10 per cent. Some of the factors related to the occurrence of failure were: long duration of labor prior to therapy, high station of the head at the onset of therapy, and the presence of intrapartum fever. It was also pointed out that when failure of pituitary stimulation occurred one could anticipate a five-fold increase in the fetal mortality rate. In an effort to overcome this 10 per cent failure rate an effort was made to search out a more physiological, and perhaps safer, method of administering this powerful drug.

Dieckmann[2] had attempted just this when he introduced "pit-sulfonate." Similarly, Pituitrin in oil had been tried in this Clinic several years ago without pronounced success. It might even be said that the intranasal method of Hofbauer[5] was a similar attempt. All of these efforts were directed at slower and more continuous absorption of the drug. It was but a small step to use pituitary extract in high dilution by continuous intravenous drip. This was tried here in 1946 and a small series of cases were reported in the previously mentioned paper. Almost simultaneously Theobald,[10] in England, used this method, not only in delayed labor but for induction as well. Further clinical trial was given the method by Stone of New York.[9] Both of these authors have expressed satisfaction with the controllability of the drug and the physiological nature of the uterine contractions engendered by high-dilution continuous intravenous drip.

Our own interest in the problem was twofold: namely, to determine the clinical efficacy of this method as compared with the intramuscular intermittent routine in the treatment of delayed labor, and to make a more definitive study of the clinical impression that the uterine contractions were more physiological during slow, continuous intravenous drip than following intramuscular injection of pituitary extract.

*Aided in part by a grant to the Johns Hopkins University from the Pharmaceutical Division, Sandoz Chemical Works, New York.

Method

In order to investigate the latter point, a number of normal patients in midlabor were submitted to study with a multichannel tokodynamometer[7, 8] while being given small intermittent intramuscular doses of pituitary extract or while being treated by the continuous intravenous drip method.

In normal labor, studies with the tokodynamometer have shown that the lower uterine segment is relatively inactive. Dilatation of the cervix is effected by a gradient of physiological activity from the fundus downward. Thus there is, in every contraction, more work done by the fundus than by the mid-zone (Fig. 1). If the calculated work done by a given portion of the fundus in any one contraction is divided by the work done in a comparable area in the mid-zone in normal labor, the resultant number, which may be regarded as a work index, will be greater than one. The larger this number is, the greater is the gradient of work between the fundus and the mid-zone, and the more efficacious labor will be. Should the reverse be found, the work index will tend to be less than one, and while the figure is actually a fraction, it can be shown graphically as a minus number. This phenomenon has been termed "reversal," and is seen frequently in abnormal labor. The administration of a single dose of pituitary extract has been observed to bring on reversal (Fig. 2). This sudden advent of abnormal labor seems to be related to dosage: if intermittent intramuscular pituitary extract in small doses is used in the treatment of delayed labor there will usually be a break-through of fundal dominance and a normal pattern will be resumed (Fig. 2). Persistent reversal is one of the factors related to pituitary extract failure in the treatment of uterine inertia. This abnormal pattern is also deleterious to the fetus for the infant and placenta can be severely squeezed when this pathological contraction pattern occurs. The result is anoxia.

Four normal women in midlabor were studied with the tokodynamometer. After a twenty-minute control period ½ minim of intramuscular Pituitrin was given. Fig. 3 shows the work index, averaged for the control period and then calculated for each pain thereafter for ten minutes. It is obvious that although there was an improvement in the frequency of the contractions, there was no improvement in the gradient of physiological work as demonstrated by the work index.

Seven similar women were given intravenous Pituitrin as follows. A dilution of 1 minim per 100 c.c. of 5 per cent saline was given at the rate of 50 c.c., or ½ minim, per thirty-minute period. The graph of the work index of these individuals is shown in Fig. 4. There is a very marked increase in the gradient of work in five of the seven individuals.

Fig. 5 shows another striking difference between the continuous intravenous method and the intramuscular method. Here both routines were employed on the same individual. The upper graph shows a short control period. One-half minim of intramuscular Pituitrin was given. There was a response within two minutes, characterized by an increase in the frequency of pains and an increase in uterine tone as indicated by the elevation of the base line. This response appears both in the fundus and miduterus. The fundal pattern is abnormal with marked irregularity and poor relaxation. The effect lasted twenty minutes and perhaps can be seen as partially effective for another ten. The patient was allowed to rest until the pattern of activity resembling that seen in the control, or preinjection period, was resumed. Then, an intravenous Pituitrin drip of standard dilution was started. The first contraction took place within one minute. Again there was an increased tone of the fundus as characterized by an elevation of the base line. The well-recognized

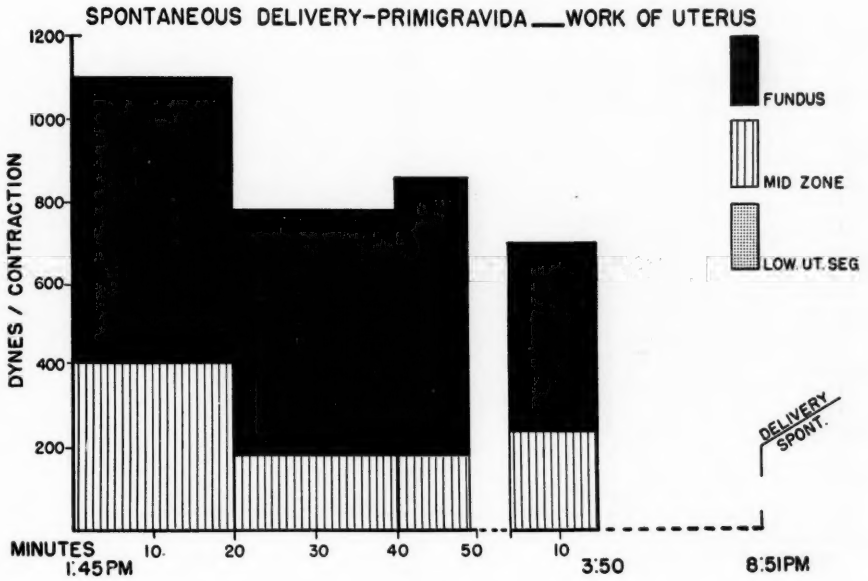

Fig. 1.—Graph of normal labor showing the work of the fundus (base line to top of black) and work of the mid-zone (base line to lower portion of the black).

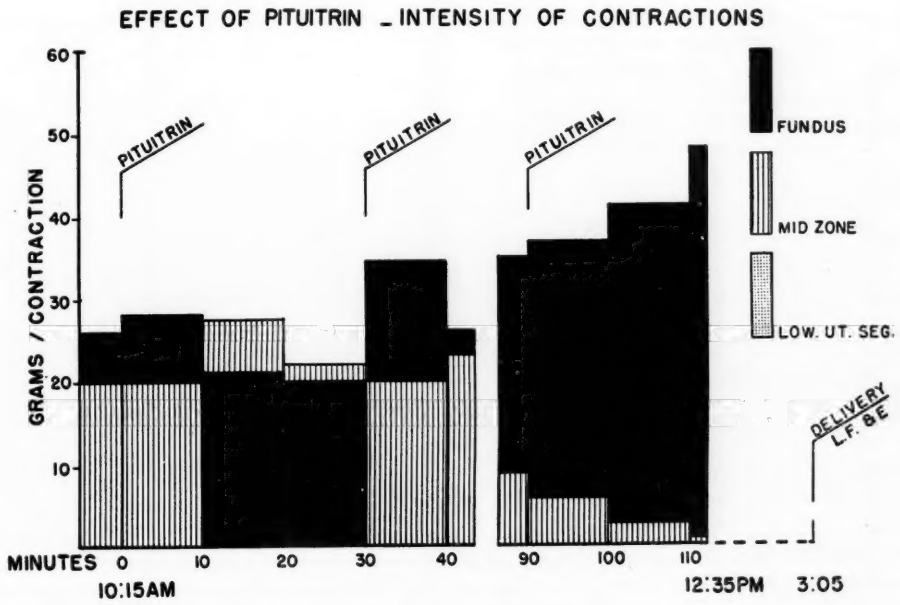

Fig. 2.—Graph showing the effect of administration of ½ minim of intramuscular Pituitrin intermittently. The reversal of work is shown at the ten-minute mark and lasts through the thirty-minute mark.

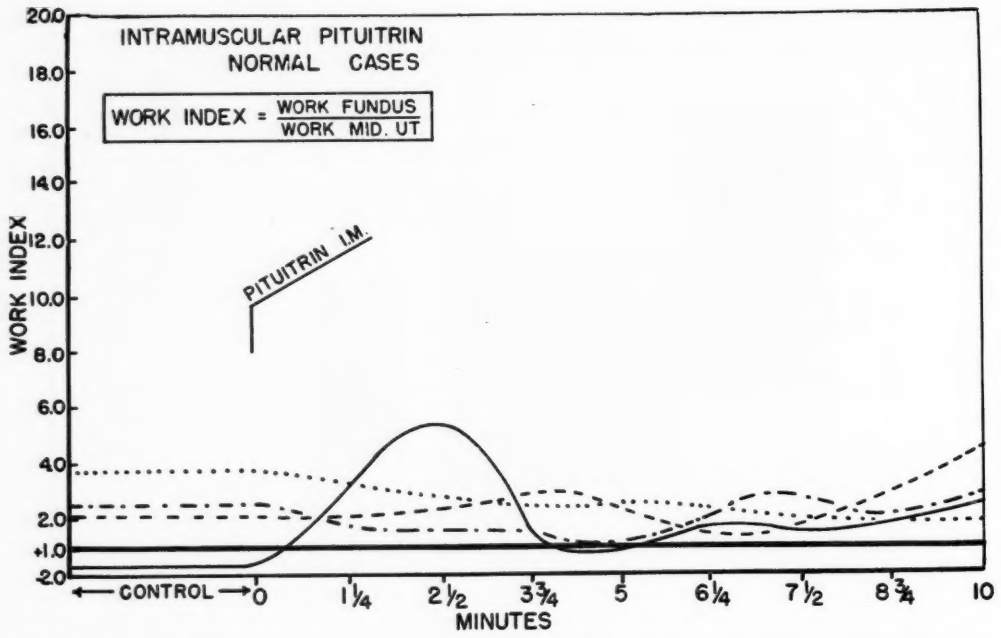

Fig. 3.—The work index in four normal cases after injection of ¼ minim of intramuscular Pituitrin.

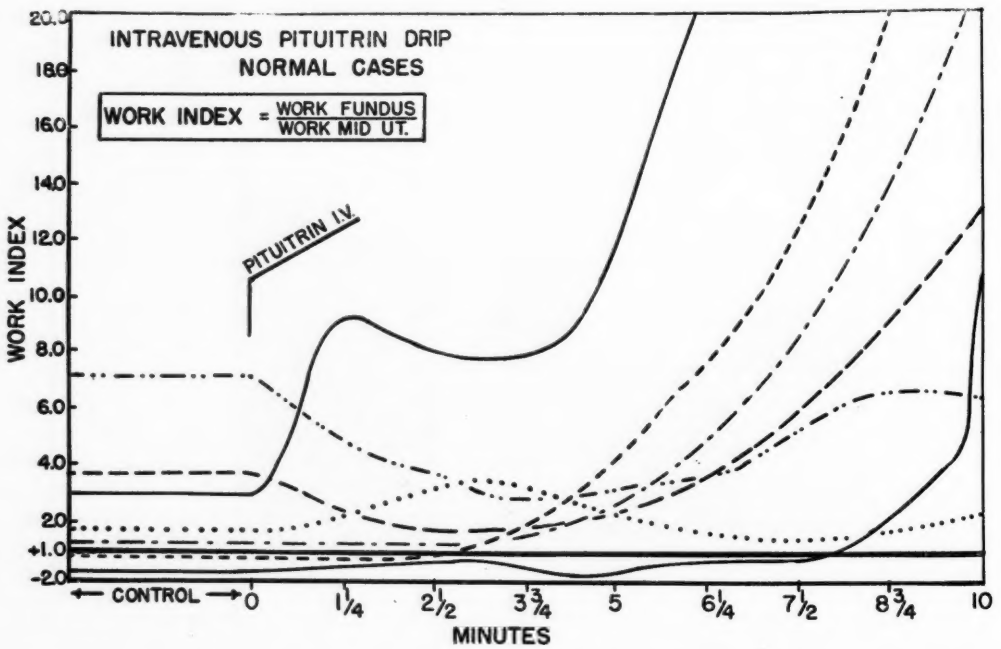

Fig. 4.—The work index in seven normal cases following the use of intravenous Pituitrin.

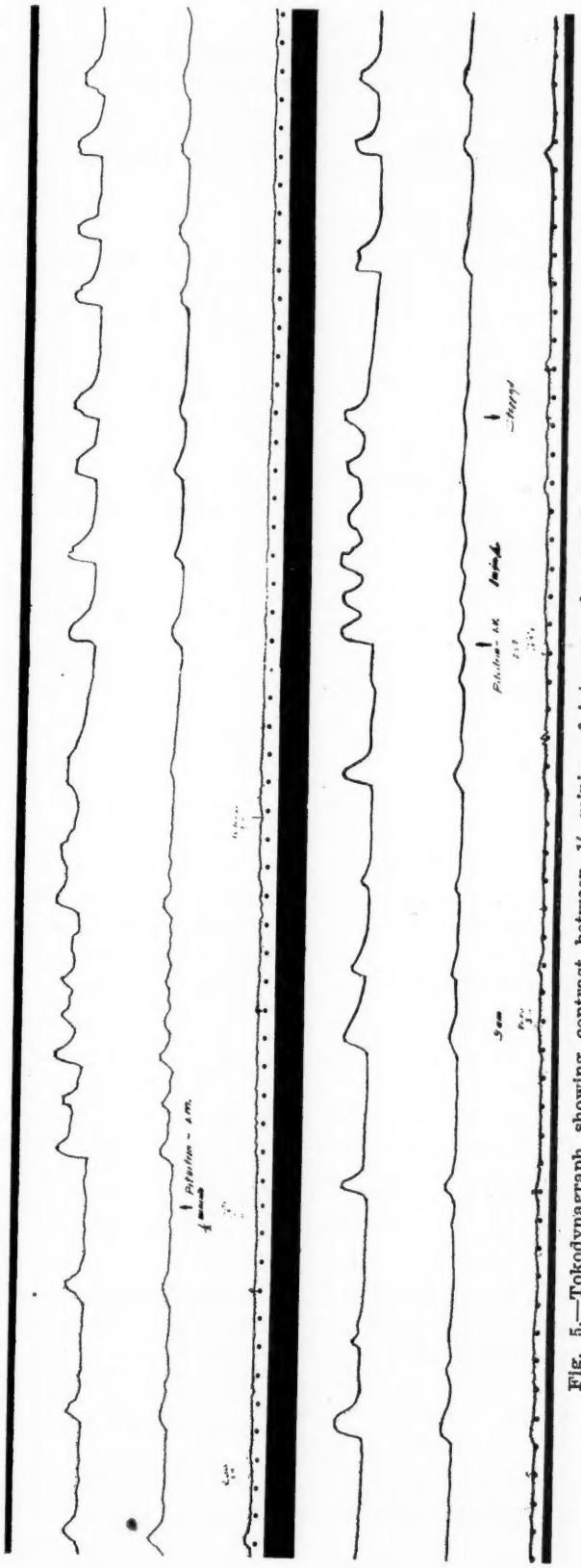

Fig. 5.—Tokodynagraph showing contrast between ½ minim of intramuscular Pituitrin and intravenous Pituitrin.

increase in frequency of contractions also occurred, but there was less activity of the miduterus than after the intramuscular injection and the physiological nature of the contraction pattern was accentuated. However, particularly striking is the prompt cessation of the drug effect when the drip was stopped. This degree of controllability of the method has been observed repeatedly.

Results

Sixty patients with secondary uterine inertia have now been treated by the continuous intravenous drip method. For purposes of clarity this type of uterine inertia has been divided into two major forms, as follows:

Incomplete Type A — Labor of more than twenty-four hours' duration with continuous and progressive cervical dilatation.

Incomplete Type B — Labor of less than twenty-four hours but with a stationary cervix of 4 cm. or more for three hours or more.

Complete Type — A combination of A and B.

All of the sixty cases were either of the complete type or the incomplete type B as shown in Table I.

Table I. Classification of Sixty Patients With Uterine Inertia

TYPE	PATIENTS	AVERAGE MINUTES CERVICAL DELAY PRIOR TO THERAPY
Incomplete A	0	0
Incomplete B	31	367
Complete	29	700

As in the previous paper, the cases were divided into "successful" and "unsuccessful" according to the efficacy of the treatment. "Successful" was thus defined as the achievement of full cervical dilatation with a lowering of the fetal head to a point where an easy low forceps could be performed (Table II). This table also shows the infant mortality rate in the two groups. The expected high rate in the "unsuccessful" group did not occur perhaps because of lessons learned in the previous experience. Four were admitted failures and cesarean section was performed. In one the patient was under the influence of an amnesic drug and was so restless the intravenous drip could not be continued. One was delivered by low forceps through an incompletely dilated cervix and the last by midforceps and Dührssen's incisions.

Table II shows a failure rate of 11.7 per cent which is nearly identical to that shown with the intramuscular method mentioned in the previous paper. Thus, while the continuous intravenous administration of the drug does not reduce the failure rate, the marked controllability and the more physiological type of contraction pattern furnished with this method are definitely advantageous.

Table II. Infant Mortality in Sixty Patients Treated With Intravenous Pituitary Extract Distributed According to Successful and Unsuccessful Outcome

	NUMBER	PER CENT	INFANT DEATHS	PER CENT	CORRECTED* INFANT DEATHS	PER CENT
Successful	53	88.3	4	7.5	2	3.7
Unsuccessful	7	11.7	0	0.0	0	0.0
Total	60	100.0	4	6.7	2	3.3

*Corrected for fetal heart heard at the onset of therapy.

The major factor influencing the success or failure of the method seemed again to be the presence or absence of intrapartum fever (Table III).

TABLE III. THE OCCURRENCE OF INTRAPARTUM FEVER IN SIXTY PATIENTS TREATED WITH INTRAVENOUS PITUITARY EXTRACT DISTRIBUTED ACCORDING TO SUCCESSFUL AND UNSUCCESSFUL OUTCOME

	PATIENTS	INTRAPARTUM FEVER	PER CENT OF PATIENTS
Successful	53	6	11.3
Unsuccessful	7	5	71.4
Total	60	11	18.3

In most instances the drug used was Pituitrin. However, in cases of elevated blood pressure Pitocin was employed. No untoward reactions were encountered with either drug when used in the low dosage indicated above. There was considerable variation in dilution, diluent, and rate of flow as the method was developed. Normal saline, saline plus 5 per cent glucose, and 5 per cent glucose were tried. No difference was observed, but perhaps from the theoretical point of view a restriction of sodium is advisable and, thus, 5 per cent glucose should be the medium of choice. The diluent itself has obviously no oxytocic effect as judged clinically and as recorded objectively with the tokodynamometer. The usual dilution has been 1 minim to 100 c.c. of diluent, or 1 c.c. of standard extract (10 cat units) to 1,500 c.c. of diluent. This solution has been allowed to flow at the rate of 50 c.c. for the first half hour and then increased, if necessary, to 100 c.c. per half hour. The number of drops necessary to give this rate of flow will vary with the apparatus used. It is probably not worth while in the majority of instances to increase the dose beyond 1 minim per half hour. Large doses are very likely to convert favorable patterns of contraction into unfavorable ones, and, furthermore, an increase in dosage does not yield a proportionate increase in effective uterine work.

Tetanic contraction was observed once. This was readily controlled by stopping the drip and when the drip was resumed the contractions were normal. The powerful, long tetanic contractions always occur when the drug is first given (D'Esopo[1] and others). Certain patterns of contractility, such as reversal, predispose to these abnormal contractions. Clinically, reversal is indicated by very painful contractions without progressive dilatation. Because of the possibility of this occurrence the initial dosage has now been reduced from ½ to ¼ minim per half hour. The rate of flow can be doubled safely after the first ten or fifteen minutes. This initial dosage may have to be further reduced as experience is gained with this technique.

Irregularity of the fetal heartbeat with slowing has been seen six times. It is extremely important that this be watched for assiduously and, when found, the drip should be stopped immediately. Usually after an hour or two the drip can be resumed, without further affecting the fetal heart rate. The low fetal mortality rate in this series of difficult obstetrical cases attests to this fact.

Most of our cases have been conducted under regional block analgesia, while the New York group have employed Demerol and scopolamine. It might seem paradoxical to administer analgesia which may delay labor, at the same time that an oxytocic substance is being administered to treat inertia; yet in long drawn-out labor, pain serves no good end and may even be deleterious to the patient. The classic experiments of Moon in experimental shock would seem to indicate this. At any rate our own results have been good, and the im-

provement in the general condition of the patient, both from the physical and morale standpoint, has been so marked that this approach seems indicated. Furthermore, if, as sometimes happens, the drug seems after a period of time to lose its effectiveness, and dilatation of the cervix ceases, one has but to raise the level of the block slightly, stop the drip, and administer a small dose of barbiturate. A rest of an hour or two ensues and, with the resumption of the drip, the results, as far as cervical dilatation are concerned, are often dramatic.

Conclusions

The action of high dilution pituitary extract administered by continuous intravenous drip has been studied from the standpoint of its effect on uterine contractility patterns and as a method of treating secondary uterine inertia.

In contrast to the intramuscular method, the same dose given by continuous intravenous method gives better tokodynamometric patterns with a far more physiological increase in work gradient.

The intravenous method offers more controllability than the intermittent intramuscular route.

Sixty cases with uterine inertia were treated by the intravenous technique using ½ minim diluted in 50 c.c. of 5 per cent glucose in the first half hour and 100 c.c. of the same mixture thereafter.

The failure rate was 11 per cent, with a total infant mortality rate of 3.3 per cent.

A reduction of the initial dosage to ¼ minim per half hour is recommended.

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Gratton, Richard R.: Unusually Large Amounts of Pitocin for the Induction of Labor, West. J. Surg. p. 84, Feb., 1949.

A clinical study on 1,211 patients in whom labor was induced by relative doses of Pitocin is presented.

A comparison of the author's schedule with that of others using Pitocin inductions indicates that he uses the drug much more freely than other clinicians. The usual dose was ½ minim every 20 minutes for two injections, 1 minim every 20 minutes for two injections, 2 minims every 20 minutes for two injections, and 3 minims every 20 minutes for two injections until labor was established. In this series there were no maternal deaths and the fetal death rate was lower than that in a group of cases of noninduced labor. Labor was successfully induced in 92 per cent of patients by the use of Pitocin alone, although some of these required as long as sixty hours before labor was induced.

William Bickers.

THE INTRAVENOUS USE OF DILUTE PITUITRIN FOR THE INDUCTION AND STIMULATION OF LABOR*

A Preliminary Report

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THE use of Pituitrin in labor dates from 1909 when Blair Bell[1] described the results which might be expected from its use in postpartum hemorrhage, and in 1911 when Hofbauer[2] suggested its use in uterine inertia. As might be expected from its ability to initiate and maintain strong and regular uterine contractions, it was immediately popularized and the indications for its employment broadened until reports of accidents caused it to be roundly condemned. So it was that in 1920 obstetrical opinion was almost unanimous in decrying the administration of the drug. Most of the objections to its use stemmed from unreliable standardization or from the use of relatively huge doses in the first and second stages of labor. Nevertheless, especially in hospitals unassociated with the large teaching centers, Pituitrin continues to be used, and, I might add from personal observation, abused, sometimes with disastrous results for both mother and fetus.

In an effort to minimize accidental overdosage it was suggested by Hofbauer[3] that the drug might be administered intranasally by inserting saturated cotton pledgets into the nostrils. This method enjoyed a certain popularity for a limited time but results were soon found to be unreliable due to individual variation in the rates of absorption. Furthermore, the method was most unpleasant to the patient. Uterine tetany and even uterine rupture occurred with intranasal administration so that in addition to its unpredictability it was found to be unsafe.[5]

The very fact that Pituitrin has been used, condemned, and again studied in the past forty years despite the dangers which have been associated with its use indicates that there is a need for a reliable method of treatment of uterine inertia and a safe and efficient method of induction of labor when obstetrical indications for the termination of pregnancy exist. Reid[4] in 1946 and Eastman[5] in 1947 acknowledged this need and showed that with appropriate safeguards in carefully selected cases, the use of Pituitrin in labor could be genuinely beneficial with no serious complications. Nevertheless, there was a certain percentage of cases in which Pituitrin failed to initiate contractions or was inadequate to maintain them at an effective level.

*Read before the New York Obstetrical Society, Jan. 11, 1949.

It was suggested to the author by Scadron[6] early in 1948 that many of the dangers and the inadequacies of Pituitrin might be overcome if the drug were suitably diluted and administered continuously by the intravenous route. Scadron, at the time, had had a high rate of success with the use of an approximately 1:500 dilution (1 minim Pituitrin in 35 c.c. of diluent) of Pituitrin in 5 per cent glucose in saline. With such a solution administered intravenously at the rate of 2 c.c. per minute, onset of contractions could reliably be predicted within five minutes, and these contractions persisted every two to three minutes resulting in rapid and effective cervical dilatation. Lately it has been learned that Theobald[7] in England has been using such a method since early 1947 with what he describes as excellent results. Theobald uses a much higher dilution of Pituitrin ranging from 1:2,500 to 1:10,000. Hellman[8] in Baltimore has also reported success with the use of intravenous Pituitrin in dilutions of 1:1,500 (0.5 minims to 50 c.c.) and notes a "graduaì and physiologic increase in uterine contractions which were maintained only so long as the solution continued to run and ceased with the cessation of the treatment."

The use of intravenous Pituitrin at Bellevue was initiated in April, 1948, and this report concerns the results obtained in thirty-two cases. Most of these cases were from the Obstetrical Service of Bellevue Hospital but some were from the author's private practice and some were collected from cases of other obstetricians in New York City on which the author collaborated. Permission to report the latter is gratefully acknowledged.

Materials and Method

The cases reported in this study were all carefully selected and fall into two groups. The first group consisted of a series of cases exhibiting primary or secondary uterine inertia in which it was felt that the occurrence of strong regular contractions was all that was necessary in order to achieve successful delivery. Cases with borderline pelves were rigidly excluded as were cases in which complicating factors existed which might make evaluation of the method difficult or inaccurate. The second group was composed of patients in whom it was felt that labor should be induced for a complication of pregnancy. The cases chosen included primiparas and multiparas. In all cases the pelvis was proved adequate by clinical examination and in doubtful instances by x-ray pelvimetry in addition.

In the cases chosen the following regimen was instituted: When decision to use intravenous Pituitrin was made the patient was immediately given sedation consisting of Demerol, 0.1 to 0.15 Gm., scopolamine 0.0004 Gm., and Seconal 0.2 Gm. Forty-five minutes to one hour later the intravenous solution consisting of Pituitrin, 15 minims in 500 c.c. 5 per cent glucose in saline (approximate dilution 1:500) was started. The clamp on the intravenous set was tightly shut until the needle was in the vein, at which time it was opened very slowly until the drop rate was determined to be 30 per minute. This rate was carefully maintained by continuous check with a stop watch, adjustments being made as they became necessary, and the solution was permitted to run until such time as caput was visible or until the cervix was fully dilated and delivery was deemed possible and desirable. In a few cases the solution was allowed to run throughout the entire second stage. In the later

cases in the series the dilution of Pituitrin was increased to 10 minims in 500 c.c. (approximately 1:750). In cases exhibiting hypertension similar dilutions of Pitocin were used in order to eliminate possible vasopressor effect.

Results

In most cases the administration of intravenous Pituitrin was followed within three to four minutes by the onset of vigorous contractions generally occurring every two to three minutes and lasting fifty to sixty seconds. In some cases not personally supervised where higher dilutions of Pituitrin were employed or where the rate was less than that described above, contractions were weaker and were more infrequent but in all these they became strong and regular when the rate of flow was increased so that a comparable amount of Pituitrin was being administered.

While the first contraction might be described as strong and while it generally lasted longer than succeeding contractions (one to two minutes) relaxation invariably occurred after this length of time except in one case which had had sedation only seven minutes before Pituitrin and in which the Pituitrin was administered at a rate of 5 c.c. per minute. This patient had regular pains after the infusion was discontinued but the first contraction lasted four minutes. No other cases suggestive of uterine tetany were observed.

In one case two small lacerations of the cervix were noted after a low forceps delivery. The infusion in this case had run for two hours and the patient had had approximately four minims of Pituitrin. There were no cases of rupture of the uterus, nor were there any deep cervical lacerations.

The total number of cases is small and it is recognized that the statistical approach is an invalid one. However, a few figures as to length of labor might not be amiss. In the twenty-two cases in which intravenous Pituitrin was used for uterine inertia the average length of labor before its employment was 27 hours (high 59, low 5.5) and the average length of labor after starting the infusion was just under four hours (high 26 hours, low 20 minutes). In the ten cases induced, the average length of labor was 2.3 hours (high 4½, low ½ hour).

The thirty-two patients whose cases are recorded here delivered thirty-three babies and there was a total of five fetal deaths. The uncorrected fetal mortality for this small series is therefore about 15 per cent. This is high as might be expected from the type of cases represented. It will be noted that all of these fetal deaths occurred in cases in which the mothers were suffering from obstetrical complications which in themselves contribute greatly to fetal mortality. The deaths will simply be listed: One baby, a second twin, was stillborn. The mother was an eclamptic who had had two antepartum convulsions and no prenatal care. She was induced with Pitocin after the convulsions. The first twin was normal. One baby was stillborn in a case of pre-eclampsia. No fetal heartbeat was heard prior to the infusion and therefore the death cannot be ascribed to Pituitrin. A third baby died twelve hours after delivery of bilateral adrenal hemorrhage. The maternal temperature was 104° F. due to a uterine infection and the fetal heartbeat was irregular prior to start of the Pituitrin infusion. A fourth baby died on the second day of pneumonia. Both mother and child had been given penicillin because of an amniotic sac infection. The fifth child died after fifteen minutes. The mother had a premature separation of the placenta and the fetal heart was irregular on admission to the hospital.

The results are summarized in Tables I and II and a few brief case reports are given.

TABLE I. SUMMARY OF RESULTS IN CASES OF UTERINE INERTIA

NAME	DILATATION OF CERVIX START OF PITUITRIN	LABOR IN HOURS AND MINUTES			TOTAL AMOUNT PITUITRIN	METHOD OF DELIVERY	RESULTS		BLOOD LOSS	PARITY	REMARKS
		BEFORE PITUITRIN	AFTER PITUITRIN	TOTAL LABOR			MOTHER	BABY			
N. M.	2+F	59:35	2:04	61:39	170 c.c. 5 M.	Mid B Barton forceps	Good	Good	100 c.c.	0	27 years old. Weak irregular pains.
M. C.	4 F	41:00	2:45	43:45	200 c.c. 4 M.	Mid B Kielland forceps	Good	Good	400 c.c.	0	28 years old. Hypertension. 4F dilatation for 12 hours.
I. C.	1 F	25:10	13:00	38:10	700 c.c. 14 M.	Mid B Barton forceps	Good	Good	200 c.c.	0	Sterility 10 years. Diabetes. Obesity (306 pounds). Hypertension.
M. S.	3 F	37:40	3:23	41:03	200 c.c. 6 M.	Breech extraction	Good	Died	150 c.c.	i	Breech. Penicillin to mother and baby.
E. T.	1 F	10:00	1:34	11:34	100 c.c. 2 M.	Low forceps	Good	Good	350 c.c.	i	Premature separation of placenta with bleeding following onset of labor.
E. L.	1+F	29:10	2:03	31:13	150 c.c. 3 M.	Low forceps	Good	Good	150 c.c.	0	2 weeks overdue. Irregular contractions 2 weeks. Desultory labor 29 hours.
P. K.	3+F	5:50	1:20	7:10	90 c.c. 3 M.	Low forceps	Good	Good	300 c.c.	i	Membranes ruptured 12 hours. Occasional weak pains. Pit. subcut. 2 doses—ineffectual.
H. K.	1+F	23:25	3:23	26:48	350 c.c. 7 M.	Mid B Kielland forceps	Good	Good	300 c.c.	0	41 years old. Infertility 8 years. Fibromyoma. Irregular pains q. 5-10 min. Poor quality throughout. Rate of flow varied.
S. S.	3 F	14:10	1:20	15:30	100 c.c. 2 M.	Low forceps	Good	Good	50 c.c.	0	Persistent R.O.P. Inertia at 3F for 6 hours.
M. D.	Edema 3½F	55:58	0:47	56:45	25 c.c. 0.5 M.	Low forceps	Good	Good	150 c.c.	0	Age 35. Infusion started 7 min. after sedation. First contr. 4 min. Infusion ran 5 min. with total 25 c.c. Contr. q. 1-2 min., 40-45 seconds.
L. W.	1 F	9:55	9:15	19:10	1,000 c.c. 20 M.	Low forceps	Good	S/B	100 c.c.	0	Pre-eclampsia. Poor pains. No F.H. Membranes ruptured. First infusion 15m/1,000 ran for 6 hr. (700 c.c.). Poor pains. Second infusion 15m/500 c.c. ran 3 hours (300 c.c.). Good contractions.

U. V.	1 F	16:00	2:06	18:06	250 c.c. 4+ M.	Low forceps	Good	Good	250 c.c.	0	Eclampsia with one convulsion. Desultory pains q. 5-10 min. 20-60 sec. Decision to use Pituitrin taken after 16 hours when patient had convulsions.
H. R.	3½F	37:15	2:28	39:43	500 c.c. 2+ M.	Spontaneous	Good	Good	150 c.c.	i	Grav. iii. No living child. Desultory irregular contractions. Pituitrin diluted 2.5 minims to 500 c.c. Rate 3.7 c.c./min.
L. R.	4 F	40:00	1:36	41:36	200 c.c. 1 M.	Low forceps	Good	Good	500 c.c.	0	Irregular desultory pains for 27 hours then 5-10 min. for 13 hours. Pituitrin 2½ m. to 500 c.c. Discontinued ½ hr. before del.
A. M.	Tough 1 F	25:10	2:20	27:30	100 c.c. 2 M.	De Wees forceps	Good	Good	500 c.c.	0	33-year-old primipara. Irregular desultory pains. Cervix tough and inelastic. Infusion ran for 90 minutes. Discontinued when patient on delivery table.
D. P.	Tough 3 F	15:00	1:20	16:20	80 c.c. 1+ M.	Low forceps	Good	Died	100 c.c.	0	Primigravida. Membranes ruptured 36 hours F.H. irregular. Patient's temp. 104° F. Given saddle block prior to infusion. Autopsy on baby—bilateral adrenal hemorrhage.
S. F.	4 F	12:00	2:29	14:29	280 c.c. 3.5 M.	Low forceps	Good	Good	300 c.c.	0	Poor weak contractions q. 7-10 minutes. Stationary cervix at 4+F for 6 hours. Infusion 6m/500 c.c. Poor result at 30 drops. Good at 60 drops.
C. T.	3½F	41:00	0:34	41:34	100 c.c. 3 M.	Spontaneous	Good	Good	100 c.c.	iii	Irregular desultory pains first 29 hours. Good pains next 10 hours. Then contractions q. 10 minutes and were ineffectual.
M. W.	Soft 1½F	11:45	2:37	14:22	500 c.c. 9 M.	Low forceps	Good	Good	200 c.c.	0	Pre-eclampsia. Hypertension 165/108. Premature baby, 3 pounds, 7 ounces.
E. D.	2 F Soft	41:00	26:00	67:00	330 c.c. 10 M.	Cesarean section	Good	Good	350 c.c.	0	Large 10 pound baby. Inaccurate estimation of size. Head engaged. Good labor with pituitrin. Cervix 3 F. Pituitrin stopped after 6:45 hr. Cesarean done 16 hours later. Ruptured membranes 6 days.
A. O'C.	1 F	23:40	2:45	26:25	250 c.c. 7.5 M.	Low forceps	Good	Good	200 c.c.	0	Weak irregular contractions 24 hours. No progress.
R. L.	2 F	15:45	0:20	16:05	30 c.c. 0.5 M.	Spontaneous	Good	Good	150 c.c.	i	Poor contractions q. 10-15 minutes.

TABLE II. SUMMARY OF RESULTS IN CASES OF INDUCTION OF LABOR

NAME	DILATATION OF CERVIX START OF PITUITRIN	LABOR, IN HOURS AND MINUTES			TOTAL AMOUNT PITUITRIN	METHOD OF DELIVERY	RESULTS		BLOOD LOSS	PARITY	REMARKS
		BEFORE PITUITRIN	AFTER PITUITRIN	TOTAL LABOR			MOTHER	BABY			
J. T.	2 F	0:00	5:30	4:30	250 c.c. 8 M.	Assisted breech	Good	Good	250 c.c.	0	Ruptured membranes 36 hr. Breech R.S.T. Term. One minim Pituitrin subcutaneously gave slight contraction.
D. N.	1+F	0:00	1:35	1:35	200 c.c. 6 M.	Twin A, mid-forceps Twin B, low forceps	Good	Twin A good Twin B still-born	150 c.c.	0	Fulminating eclampsia. Two convulsions. 36 weeks' gestation. No antepartum care.
G. B.	3+F	0:00	1:59	1:59	230 c.c. 4+ M.	Spontaneous	Good	Good	100 c.c.	ii	Grav. vii. Widely dilated cervix 39 weeks. Two minims Pituitrin subcutaneously failed to cause contractions.
C. V.	Thick Closed	0:00	3:01	3:01	250 c.c. 4 M.	Spontaneous	Good	Good	100 c.c.	i	Previous hypertension in pregnancy. Hypertension 190/110 increasing ++++ albumin 39 weeks' gestation.
S. Z.	1 F Soft	0:00	2:00	2:00	85 c.c. 2.5 M.	Kielland forceps	Good	Good	Scant	0	Membranes ruptured 18 hours. Occasional mild contractions but no dilatation. First contraction prolonged because of rapid flow of solution.
E. N.	2 F Soft	0:45	0:30	1:15	60 c.c. 2 M.	Spontaneous	Good	Died	Scant	iii	Premature separation of placenta. F.H. irregular 72-100 from admission. Vague pains on admission.
E. S.	2 F Thick	3:50	0:50	4:40	50 c.c. 1.5 M.	Low forceps	Good	Good	200 c.c.	i	False labor 2 weeks. Pains before infusion every 10 minutes. Irregular quality.
S. W.	Thick 1 F	0:00	4:25	4:25	250 c.c. 7.5 M.	Spontaneous	Good	Good	150 c.c.	v	False labor one week.
R. K.	1 F Thick	0:00	4:10	4:10	120 c.c. 3.5 M.	Spontaneous	Good	Good	200 c.c.	i	False labor 2 weeks. Previous delivery 36 hr. Labor—high forceps. 3° lac. Baby 7 pounds, 3 ounces.
S. B.	2 F Thick	2:00	0:53	2:53	100 c.c. 1.5 M.	Spontaneous	Good	Good	150 c.c.	ii	2 therapeutic abortions for vomiting. Severe vomiting this pregnancy. False labor 2 weeks. Occasional irregular contractions 2 hours.

Case Reports

CASE 1.—N. M., aged 27 years, para 0, gravida i. The patient's pregnancy was normal throughout. The pelvis was large platypelloid as determined by x-ray pelvimetry and was considered adequate for this baby. Labor started at 10 A.M. of April 2, 1948, the pains being of poor quality every fifteen minutes. The patient was given frequent sedation for rest but at 8:30 P.M. of April 4 the cervix was only two and one-half fingers dilated and the pains were still of poor quality. At this time it was decided to use intravenous Pituitrin and the patient was given Nembutal 0.1 Gm., Demerol 0.1 Gm., and scopolamine 0.0004 Gm. At 9:35 P.M. the infusion containing 15 minims of Pituitrin in 500 c.c. of saline was started. Within two minutes the patient had her first pain lasting 40 to 55 seconds; thereafter they occurred every one to two minutes. At 11 P.M. the cervix was fully dilated, the head being 2 cm. below the spines in persistent transverse position. At 11:39 P.M. Barton Forceps were applied and a normal female infant was delivered. The baby breathed and cried spontaneously. The placenta was delivered in three minutes without incident, the blood loss being 100 c.c. Both mother and child made an uneventful recovery.

CASE 2.—D. N., 23 years of age, para 0, gravida i, 36 weeks' gestation, twin pregnancy. The patient was admitted to the hospital for edema, hypertension, and four plus albuminuria. In spite of sedation, bed rest, and the usual toxemia regime, symptoms became aggravated and the patient had two generalized convulsions. Vaginal examination after the last convulsion revealed a one and one-half finger thin cervix and at 9:15 A.M. of Sept. 8, 1948, the patient was given sedation consisting of Demerol 0.1 Gm., Sodium Amytal 0.25 Gm., and scopolamine 0.0004 Gm. At 10:15 A.M. intravenous Pitocin was started, a dilution of 30 minims of Pitocin in 1,000 c.c. of 10 per cent glucose in distilled water. Strong pains began in one minute and occurred every two minutes thereafter lasting thirty seconds. No tetany was noted. At 11:35 A.M. the cervix was fully dilated and the infusion was discontinued at 11:38 A.M. An estimated 6 minims of Pitocin were used in approximately 200 c.c. of diluent. At 11:45 A.M. Twin A weighing 5 pounds, 7 ounces was delivered by midforceps and at 11:50 Twin B was born by low forceps. The latter twin was stillborn. The fundus remained well contracted and the surviving baby made an uneventful recovery.

CASE 3.—E. D., 21 years of age, para 0, gravida i, clinically ample gynecoid pelvis. This patient was admitted to the obstetrical service on Nov. 6, 1948, with a history of rupture of the membranes since Nov. 3, 1948. She was immediately placed on penicillin as a prophylactic measure and at 6:15 P.M. that evening began a desultory labor characterized by infrequent pains of poor quality. These persisted for the next forty hours at which time vaginal examination revealed a two-finger thin, soft cervix with the head in right occipitoposterior position 1 cm. below the spines. The head was freely movable and it was felt that with good pains the patient should deliver from below. Sedation was administered at 10:15 A.M. November 8 and at 10:45 A.M. pituitrin infusion was started, the dilution being 15 minims in 500 c.c. of 5 per cent glucose in saline. Within two minutes the patient had a strong pain lasting fifty seconds and this was followed by contractions every three minutes lasting thirty to fifty seconds. The contractions were characterized by a rapid rise to peak intensity and a long slow decline. The intravenous infusion continued to run until 5:30 P.M. at a rate of somewhat less than 1 c.c. per minute, 330 c.c. equivalent to 10 minims of Pituitrin being used. At this time the cervix was three fingers dilated but because of the lack of progress the intravenous infusion was discontinued and the patient was allowed to rest. The contractions subsided almost immediately until 5:30 A.M. of November 9, when an occasional moderate contraction was noted. The cervix remained at three fingers' dilatation. At 10 A.M. reevaluation of the patient was undertaken and it was decided that the size of the fetus had been underestimated and that cesarean section was indicated. It was noted that the anterior shoulder of the fetus was overriding the symphysis and that this was undoubtedly preventing the descent of the head. At 12:28 P.M. of Nov. 9, 1948, the patient was delivered of a living

10 pounds normal male infant by low flap cesarean section. Inspection of the lower uterine segment at the time of operation revealed it to be uninjured. Mother and baby did well until discharge. In this case it is obvious that a mistake in judgment was made. While the pelvis was large, the size of the fetus was misjudged and it was of course not a proper case in which to use Pituitrin in any form. We were fortunate that no serious complication occurred. This case is described merely to emphasize how difficult it may be in certain instances to evaluate the situation accurately.

Discussion

It appears from the available evidence to date that the use of intravenous Pituitrin is an effective method of stimulating or initiating pains in patients in labor or near term. Theobald[7] used intravenous Pituitrin in twenty-nine cases and in the nine cases which he reports in detail (five cases of induction and four of inertia) observed no accidents attributable to its use although his dilution of the drug was considerably higher than that which we use. Hellman[8] using a 1:1,500 dilution in forty-three cases reports thirty-six "successful" results and mentions that in seven cases the results were "unsuccessful" regarding the initiation of contractions. He encountered no fetal or maternal mortality in the forty-three cases. He mentions that the failure rate, 16.3 per cent, is not significantly different for this small series from the failure rate of 11.7 per cent noted by Eastman[5] in a large series of cases given intramuscular Pituitrin. He therefore states that intravenous pituitrin did not increase the "success rate."

In the cases reported here we have been uniformly successful in stimulating and maintaining labor until its eventual culmination in delivery. Further, in no case have we seen any complication which might be engendered by overstimulation of the pregnant uterus.

We have been impressed with the rapidity with which contractions are stimulated, with the rhythmicity with which they are maintained, and more particularly with the definite relaxation which occurs between contractions.

It would seem that the intravenous method is the logical choice for the administration of Pituitrin for a number of reasons. These may be summarized as follows:

1. The amount of Pituitrin in the blood stream at any one time is definitely known and can be reduced or increased at will by simple adjustment of rate of flow of the solution or by dilution of the drug. Individual variation in rate of absorption is thus eliminated.

2. It has been observed that contractions cease when the solution is discontinued thus providing a large factor of safety.

3. The amount of Pituitrin used is minute and is administered over a long period of time.

4. Since the blood level of Pituitrin is relatively constant the contractions occur relatively regularly and are therefore more effective in dilating the crevix. With other methods of administration, the Pituitrin levels may be presumed to be irregular and therefore contractions may vary widely in interval and amplitude. In addition sudden surges in the Pituitrin level when it is administered subcutaneously would be more likely to cause rupture of the uterus.

While we have had no unpleasant experiences with the dilutions of Pituitrin used (i.e., 1:500 and 1:750) it is nevertheless true that higher dilutions are effective. As has been stated, Hellman[8] used 1:1,500 and Theobald[7] in his later cases 1:10,000. The latter calculates Pituitrin concentration in the plasma necessary to initiate labor as $1:3.75 \times 10^6$, an extremely minute

amount. On the other hand, Scadron[6] has noted no accidents from the use of concentrations as strong as 1:375. It may be that the "failure rate" mentioned by Hellman can be reduced without undue risk by the use of the more concentrated solutions.

In the last few cases the intravenous solution has been continued throughout delivery and the third stage. In these cases prompt separation of the placenta occurred followed by firm contraction of the uterus. It seems that an actively contracting uterus may render less likely the upward displacement of the head incidental to the application of forceps and further that the continuation of the medication may reduce the incidence of postpartum atony of the uterus so common in cases of primary or secondary inertia.

It would be foolish to draw any final conclusions from the small number of cases reported but the evidence presented suggests that further experimentation with the intravenous method is likely to prove exceedingly rewarding.

Summary and Conclusions

A method of administering Pituitrin intravenously in cases of inertia uteri and for induction of labor is described.

Illustrative case reports and the results in thirty-two cases are described.

Labor was initiated or stimulated in all the cases reported. Labor following intravenous Pituitrin stimulation was in general rapid without being violent.

No accidents of any sort were encountered.

There were five fetal deaths in this series of thirty-two cases, all of them occurring in infants prejudiced by a complication of pregnancy. In no case was it probable that the Pituitrin was responsible for the fetal death.

Further use of the method is definitely indicated and should be made before any valid conclusions are drawn.

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PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

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(From the Free Hospital for Women)

PRIMARY carcinoma of the Fallopian tube is reputedly one of the rarest of female genital cancers. It was first described by Raymond in 1847 and later by Rokitansky[1] in 1861. In spite of these earlier descriptions the majority of writers give priority on this subject to Orthmann[2] who thoroughly described the disease in 1888.

To date approximately 470 cases have been reported in the literature. In 1945 Mitchell and Mohler[3] compiled 449 cases in a comprehensive review of the literature. To these can now be added the one case of Brea,[4] the sixteen cases of Lofgren,[5] and the present series of twelve cases, making a total of 478 cases. It is the purpose of this paper to compare the experiences of these investigators of this disease with that of the Free Hospital for Women.

Incidence

The incidence of this condition varies at different medical centers. At the Free Hospital for Women there have been twelve primary carcinomas of the Fallopian tube out of 3,878 primary malignant lesions of the female genital tract in the 90,611 admissions from 1903 to 1948, an incidence of 0.31 per cent of primary malignant tumors. This appears to be the second largest series that has occurred in any one clinic, as recorded in Table I.

Table I. Incidence of Carcinoma of Fallopian Tube

Author	Clinic	Years Covered	Gynecologic Admissions	Salpingectomies	Primary Malignant Lesions	Cases
Fullerton[6]	Cleveland	13	22,330			4
Ayre[7]	Royal Victoria		30,000			2
Auspach[8]			19,439			1
Tuta, Stuhr[9]	Johns Hopkins	50				11
Bancroft[10]	Middlesex	25				4
Mitchell[3]	Philadelphia	47		6,747		1
Haupt[31]	Bonn				1,361	3 (0.22%)
Lofgren[5]	Mayo	40			10,000	16 (0.16%)
Hu, Taymor and Hertig	Free Hospital	45	90,611		3,878	12 (0.31%)

Material and Methods

This study is based upon a review of the clinical and pathological records of the Free Hospital for Women, Brookline, Mass. The histories of private patients were obtained by sending questionnaires to the respective doctors.

There were fifty-five cases of carcinoma, either primary or metastatic, involving the tubes. The criteria we used for differentiating between these two types of neoplasms are as follows:

1. Grossly, the main tumor is in the tube.
2. Microscopically, chiefly the mucosa should be involved, and should show a papillary pattern.
3. If the tubal wall is found to be involved to a great extent, the transition between benign and malignant tubal epithelium should be demonstrable.

Using this method we were able to find sixteen cases and divided them into three groups:

1. Frank primary carcinoma of the tube (twelve cases).
2. Carcinoma in situ of the tube (one case).
3. Double primary carcinoma of the tubes and ovaries (three cases).

Since the status of the cases in the latter two groups may be open to some question, we have utilized only the twelve cases of Group 1 as the basis of our study.

Clinical Data

Age.—The youngest patient in our series was 34, the oldest 67 years old. The majority of our patients were in the middle years of life, that is between the ages of 40 and 65 years. Nevertheless, in the literature there were recorded three cases involving 18-year-old girls.[11, 12] Fullerton[6] in 1940 reported the oldest patient, 80 years of age.

Parity and Gravidity.—One patient in this series of twelve cases was not married and only three of the eleven married patients were childless. The most fertile patient of this group had had four children. Many authors have mentioned that sterility is frequently associated with carcinoma of the tube. Sanger and Barth[13] reported a 44 per cent correlation, Curtis[14] 32 per cent, and Vest[15] 29 per cent. Our figure was 27 per cent.

Menstrual History.—There were eight postmenopausal patients and four patients within the childbearing age. Of the postmenopausal patients, three had a return of definite flow while five had spotting. Two of the four patients within the childbearing age had normal periods, one had irregular menstruation, and in one no menstrual data was available. The duration of the abnormal flow in the entire series varied from two to eighteen months. One patient 56 years of age complained of postcoital bleeding, and another postmenopausal patient had periodic flowing every seven to fourteen days.

Discharge.—Most authors have stated that vaginal discharge is the commonest symptom. This condition was present in ten of the twelve cases of this series. The character and amount varied considerably. Five of the ten complained of a bloody discharge, two were serosanguinous, one was creamy, and the remaining two unqualified. Addis[16] reported three cases all associated with a clear watery discharge. Cullen and Daniel described cases with a discharge amounting to as much as one liter a day. The duration of discharge varied from nine to twelve months. The patient in one of the cases Wechsler[17] reviewed was said to have had a discharge for twenty years.

Hydrops Tubae Profluens.—Since Latzko[18] in 1915 called attention to this symptom of relief of pain on disappearance of a mass accompanied by profuse vaginal discharge as a typical finding in carcinoma of the tube, many other writers have reported similar findings but with incidences that have varied considerably. Peham[19] was able to find only five in his sixty-three collected cases. He emphasized that the symptom is valuable in calling attention to a

diseased tube, but it is not pathognomonic of carcinoma. Pankow[20] stated in his textbook that it occurred more often with hydrosalpinx. We had only one patient who noted a rounded low abdominal tumor that disappeared with the onset of a period. None of our remaining patients described any symptoms similar to hydrops tubae profluens. Hobbs[21] stated that *hemohydrops tubae profluens* should add weight to the diagnosis of primary carcinoma of the tube, but we were unable to reconstruct such a syndrome from the complaints of any of our patients.

Pain.—Pain in the lower quadrants, usually on the side of tubal involvement, was the second most common symptom. It was the chief complaint in six of the twelve cases. Two patients complained of sharp, crampy, lower quadrant pain associated with tubo-ovarian masses on the same side. Two had severe backache, and one of these had a tubal mass adherent to the posterior surface of the uterus. Thus we see that the location of the pain is dependent upon the direction of tumor extension. The time elapsing between onset of pain and admission was shorter than any other symptom, ranging from five days to one and one-half years.

Tumor Mass.—A palpable mass was found in nearly all cases, although only three of our patients noted any enlargement of the abdomen themselves. Peham[19] emphasized the fact that the enlargement of the abdomen was usually due to an associated fibroid or ovarian cyst which was pushed upward by the tumor. This is an important point to be considered in clinically estimating the actual tumor size. The masses described were for the most part firm and irregular, varying from 3 cm. in diameter to one reaching to the umbilicus. One was described as cystic. Only one was movable, the remainder were fixed. All were located in the lateral quadrants except for one in the cul-de-sac.

In the literature ascites was associated with carcinoma in as high as 10 per cent of cases.[17] In none of our cases was ascites recorded.

Diagnosis

In reviewing the literature it was found that a preoperative diagnosis was made on very few occasions. Baron[1] states that Dannreuther was the first to make a correct preoperative diagnosis. Hobbs[21] reported a case diagnosed as a probable carcinoma of the Fallopian tube because of the presence of the so-called typical symptom of hydrops tubae profluens. McGoldrick[22] in reviewing 376 cases in the literature was able to find only one correctly diagnosed preoperatively, that by Martzloff. In the series at the Free Hospital one case was diagnosed preoperatively by Dr. George Van S. Smith as a probable primary carcinoma of the tube. The remainder of the cases were diagnosed as ovarian cysts, with or without twisted pedicles, salpingo-oophoritis, or fibroid tumors.

Factors making preoperative diagnosis almost impossible are many. The most paramount of these are the lack of characteristic history, symptoms, or physical findings. There is a frequent association with more common diseases of the pelvic organs the presence of which may mask the pelvic findings due primarily to carcinoma of the tube. The most notable example is the common coexistence of chronic salpingitis, either unilateral or bilateral, which produces multiple adhesions between the pelvic organs, thereby making correct appraisal obviously impossible.

In an attempt to offset these difficulties many suggestions have been advanced, some of which may be mentioned for historical interest rather than as recommended diagnostic procedures. Falk[23] in 1898 recommended cul-de-sac

puncture in order to withdraw the contents of a carcinomatous tube adherent to the pelvic peritoneum. If the aspirated fluid is hemorrhagic, noncolloid, mixed with tissue debris, and shows polyhedric fatty degenerated cells, one should think of the possible presence of malignant tumors. On the other hand, Peham[19] believed that it was almost impossible to make a correct diagnosis even with the gross specimen, and he felt that Falk's procedure was too dangerous in view of the equivocal information obtained.

Martzloff recommended salpingography as a useful diagnostic procedure, although Hobbs[21] and others considered this procedure unsafe due to possible dissemination of cancer cells into the peritoneal cavity. Martzloff, however, felt that the need for early diagnosis probably outweighed this potential hazard.

Meigs[24] as far back as 1934 emphasized the importance of collecting every bit of discharge. This should be filtered and examined microscopically. This is in keeping with the present day trend of the Papanicolaou staining of the vaginal smear. The routine use of this procedure may result in the discovery of earlier cases of primary cancer of the tube.

One from our own series (Case 11) is such a case in point, and was reported by Isbell and associates[25] in 1946 in a presentation of the correlation between vaginal smear and tissue diagnosis at the free Hospital for Women. The patient, 67 years of age, complained of periodic vaginal bleeding, every one to two weeks. Endometrial curettings revealed an endometrial polyp with marked atrophy of the endometrium. Vaginal smear was positive. Six months later complete hysterectomy and bilateral salpingo-oophorectomy were carried out because of the persistent postmenopausal bleeding despite negative biopsy. The pathological report was papillary carcinoma, Grade II, of the right tube, anaplasia of the left tube, chronic cervicitis, and carcinoma in situ of the endometrium. Since in their series only one in seven cases of carcinoma in situ of the endometrium had a previous positive vaginal smear, Isbell and his co-workers felt that the malignant cells of this vaginal smear had definitely arisen from the papillary carcinoma of the tube. Although this was not a definitely diagnosed case by the vaginal smear method, it suggests the usefulness of this procedure.

Gross Pathology

The gross findings were extremely variable. In nine of the twelve cases a complete gross description was available. The tubes varied from moderately enlarged nodular structures 2 cm. in diameter (Fig. 1) to large sausage-like structures 17 cm. in diameter. Four of the cases were described as tubo-ovarian masses, and in all but one case there were numerous adhesions to other pelvic organs. The finding of these latter two conditions makes the differential diagnosis from hydro- or pyosalpinx of pelvic inflammatory disease extremely difficult. In five cases friable tumor tissue extruding from the fimbriated end of the tube was described. Upon opening the lumen the granular, friable, grayish tumor mass was always located in the distal third of the tube. In one instance, however, the tumor was described as rocklike although still friable. Fluid was also often present in the lumen and was usually bloody, although on occasion it was purulent or caseous. The last case in our series, Case 12, presents the typical gross findings (Fig. 1).

In six cases the tumor was found to be in the right tube, and in five cases in the left. In only one case was the condition found to be bilateral, although in another instance anaplasia of the epithelium of the opposite tube was found. Vest[15] stated that there is a possibility of transmigration of material from one tube to another as with the fertilized ovum. In our series the opposite tube was occluded in ten cases.

Salpingitis, the most commonly associated condition, was present in all except three of the cases and was of follicular type in seven of these nine patients. Fibroid tumors were found on five occasions, adenomyosis and ovarian cysts each twice, and endometrial carcinoma in situ once.

Metastases at the time of first operation were found in the ovary alone in five instances, in the ovary and endometrium once, and once in the opposite tube. Five cases had no metastases at time of operation. Meigs[24] has stated that tubal carcinoma metastasizes to the vagina in about 60 per cent of cases. At our follow-up clinic two vaginal metastases were found twenty-seven days and seventeen months after operation. Liver metastases were found in one case and spread to the opposite tube was found a year later in another. Pelvic metastases occurred on two occasions twelve and seventeen months, respectively, after operation; and in the latter case omental spread was found ten months later.

Fig. 1.—Carcinoma of the tube, gross pathology.

Microscopic Findings and Classification

The varieties of classification are almost as numerous as the actual reviews in the literature. The various differences stem from the fact that the growth pattern may result in two different forms, a papillary and an alveolar, with various gradations, or combinations of the two. Whether or not the alveolar type represents a separate group is the point of difference. The classification most widely accepted seems to be the one first put forth by Sanger and Barth[17] and supported by Lipschitz,[26] Wharton,[27] Krock, Robert Myer,[28] and many others, to the effect that the predominant type of this tumor is papillary. They further hold that the alveolar pattern is merely a later stage of this growth and is not an inherently distinct type. Others, such as Friedenheim,[29] divide the neoplasms into two separate types, a papillary or papillary alveolar group, and a definitely alveolar type. This classification finds support in those alveolar types in which absolutely no papillary projections can be observed. We have one such case in our series. Still others, Peham,[19] Hofbauer and Adlehard, use the terms alveolar and papillary-alveo-

lar to describe their distinct classes. Falk,[23] finally, describes three forms: (1) benign papilloma, (2) malignant papilloma, and (3) papillary carcinoma.

Our findings seem to agree more closely with those of Sanger, i.e., the alveolar type is merely a later stage of growth of the more fundamental papillary pattern. Utilizing this principle we have used the following classification:

Fig. 2.

Fig. 3.

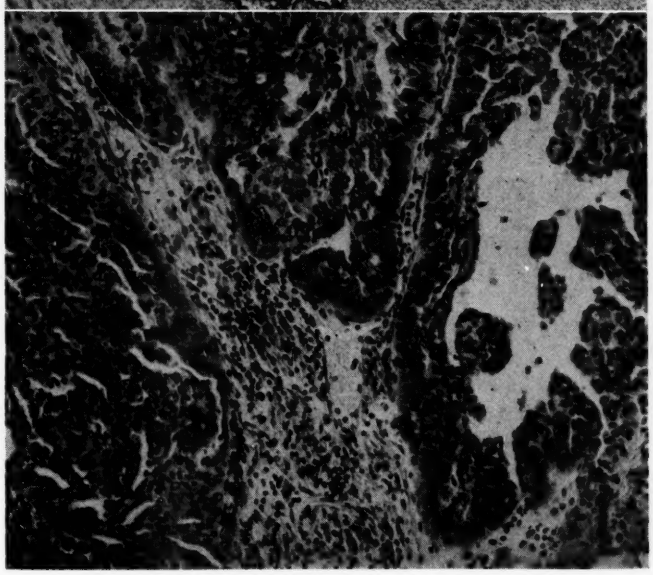

Fig. 2.—Grade I, showing confinement to lumen and papillary nature. (×50.)
Fig. 3.—Grade I, well-differentiated cells with few mitoses. (×200.)

Grade I. *Papillary.* (Figs. 2 and 3.) The pure papillary growth is confined to the lumen of the tube. The transition between normal and malignant

epithelium is clearly seen. The high-power view shows the cells to be fairly well differentiated, columnar in shape, and mitotic figures are scanty.

Grade II. *Papillary-Alveolar.* (Fig. 4.) There is beginning glandular formation and invasion of the tubal wall. The individual cells are undifferentiated with a moderate number of mitotic figures.

Fig. 4.

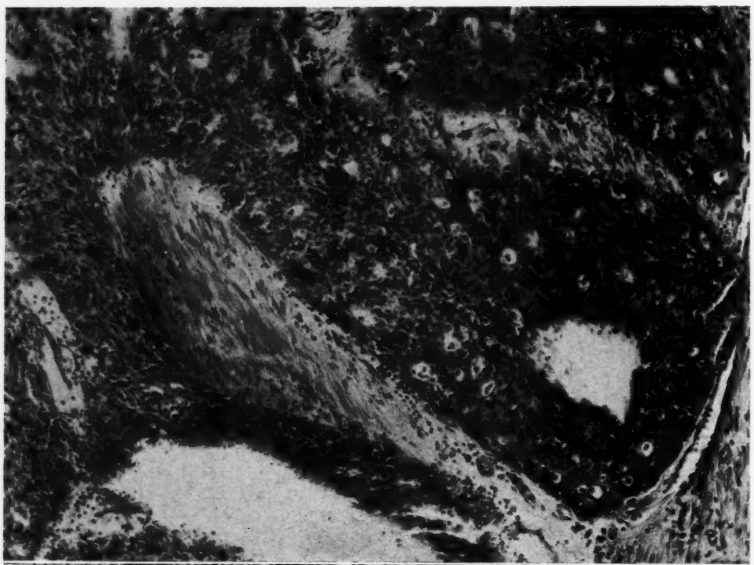

Fig. 5.

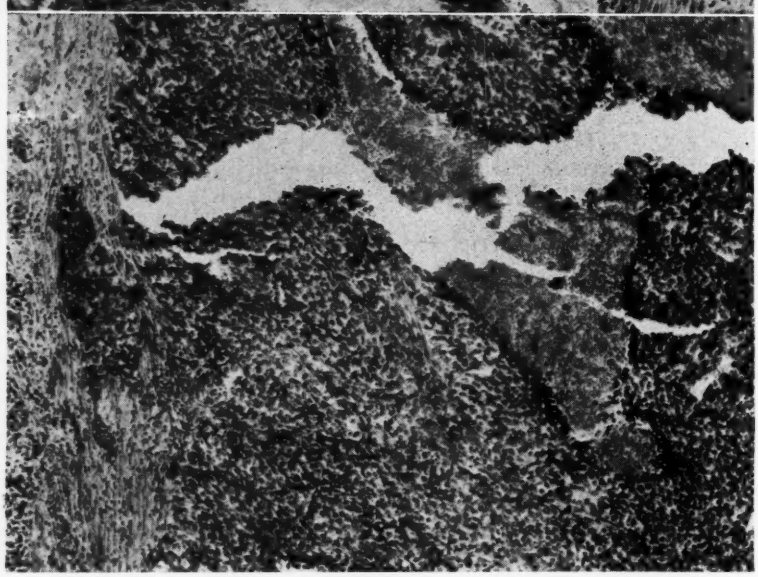

Fig. 4.—Grade II, papillary alveolar. (×150.)

Fig. 5.—Grade III, alveolar-medullary, showing anaplastic cells invading the wall of the tube. (×150.)

Grade III. *Alveolar-Medullary.* (Fig. 5.) The growth is more solid with lack of papillary projections, and the cells are arranged in a medullary or glandular pattern. There is definite invasion in the lymphatic vessels of

the tubal wall. Under higher power the cells are seen to be poorly differentiated, show vacuolization, and abundant and atypical mitoses.

Using this classification we placed two cases in Grade I, five in Grade II, and five in Grade III. The majority of writers hold that there is little if any correlation between the degree of histological malignancy and the prognosis of the disease. One of us (A. T. H.) knowing nothing about the clinical histories, and utilizing the above classification, placed the slides in their respective grades. We then found a relatively good correlation between histological grading and survival of patients. Of those classified as Grade I, one was living twenty-eight years after operation when last heard from, and the other was just operated upon in 1947. Four of the five patients whose cases were classified as Grade II were living ten, nine, nine, and one and one-half years, respectively, after operation when last heard from. The last patient in this group died after one year. All of the patients with a classification of Grade III are dead, surviving only twenty-seven, twenty-four, seventeen, ten, and five months after operation. These results are shown in Fig. 6.

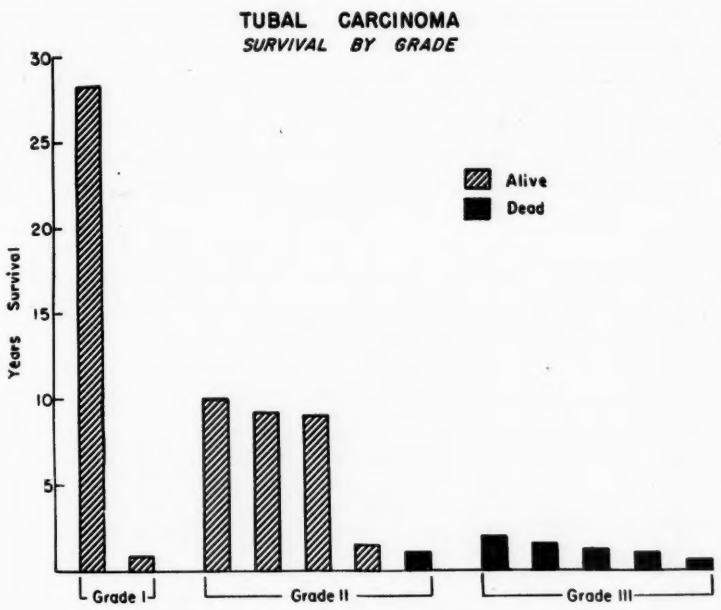

Fig. 6.—Tubal carcinoma, survival by grade.

Case Report

Case 12, the last in the series, was the stimulus for this report, and will be presented in detail.

M. M., aged 56 years, was admitted on May 5, 1947, with a history of irregular and infrequent menstrual periods during the past year accompanied by itching and hot flashes. Three months prior to admission the patient began to bleed after intercourse. This continued for four days as dark red blood that stopped for a few days and then began again. Since then there had been a daily discharge of dark blood with occasional clots. The discharge was sometimes watery in consistency. The patient had lost ten pounds in the past four months but had no pain. Physical examination was not remarkable. The uterus was anterior and slightly enlarged with thickening in the right vault. On the day after admission the patient had a complete hysterectomy, bilateral salpingo-oophorectomy, appendectomy, and lysis of adhesions.

Gross pathology (Fig. 1) showed the uterus to be slightly enlarged and covered with numerous adhesions. Both ovaries were normal in appearance but atrophic. The right tube was elongated and enlarged in a retort-shaped fashion. The left tube was knuckled across the top of the fundus by dense adhesions. Cut section through the left tube showed it to be filled with a grayish friable material.

Microscopic sections showed adenomyosis of the uterus, chronic follicular salpingitis of the right tube. Sections through the left tube (Figs. 2 and 3) showed a typical Grade I primary carcinoma of the tube. The transition between normal and abnormal epithelium was clearly seen. The growth was purely papillary in nature. The cells were fairly well differentiated and mitotic figures were few.

The patient was operated upon in May, 1947. She was well when seen one year later. Her prognosis would appear to be excellent.

Treatment and Prognosis

Seven cases were treated by supravaginal hysterectomy and bilateral salpingo-oophorectomy, three of which had additional postoperative therapy in the form of radium, x-ray treatments, or both. One case, deemed inoperable, had only a supravaginal hysterectomy and radiation. The remaining four cases were treated with complete hysterectomy, bilateral salpingo-oophorectomy, and all but one had postoperative x-ray treatment. The survival of these patients, together with the type of treatment and histological grading, are tabulated in Table II. The routine use of panhysterectomy is of too recent origin and our series too small to draw any definite conclusions as to its beneficial results.

TABLE II. CARCINOMA OF THE FALLOPIAN TUBE: GRADING, OPERATION, AND SURVIVAL

CASE NO.	YEAR	GRADE	OPERATION	SURVIVAL
1	1909	II	SV Hysterectomy, Bil. S.O.†	1 year
2	1913	I	SV Hysterectomy, Bil. S.O.	28 years*
3	1927	II	SV Hysterectomy, Rt. S.O., Radiation	10 years*
4	1927	III	SV Hysterectomy, Bil. S.O.	5 months
5	1931	III	SV Hysterectomy, Bil. S.O.	17 months
6	1933	III	SV Hysterectomy, Radiation	10 months
7	1936	III	SV Hysterectomy, Bil. S.O., Radiation	27 months
8	1938	II	SV Hysterectomy, Bil. S.O., Radiation	9 years*
9	1938	III	Panhysterectomy, Bil. S.O., Radiation	2 years
10	1939	II	Panhysterectomy, Bil. S.O.	9 years
11	1946	II	Panhysterectomy, Bil. S.O., Radiation	18 months*
12	1947	I	Panhysterectomy, Bil. S.O., Radiation	1 year*

*Living when last heard from.
†Supravaginal hysterectomy, bilateral salpingo-oophorectomy.

Excluding two cases operated upon too recently, our five-year survival rate was 40 per cent. This rate compared favorably with the survival rates of other observers. The reports are difficult to compare because they stretch out over long periods of time. It would appear from the results that today's surgeon is operating earlier and more radically, with more favorable results. Wechsler[17] collected 200 cases in which only six patients survived more than three years. Haupt[31] reviewed 321 in 1933. Only six of these survived eight years. On the other hand, Wharton's[27] fourteen cases from Johns Hopkins had a three-year survival of 20 per cent.

These figures only accentuate the obvious fact that early diagnosis and radical surgery are the treatment of choice. One may state that here is an argument for radical surgery in any patient near or past the menopause who presents symptoms of adnexal disease. We also fully agree with Peham[19] who

emphasized the fact that since the establishment of the modern expectant treatment for chronic pelvic inflammatory disease, a number of carcinomas of the Fallopian tubes will go undiagnosed until they reach an incurable stage.

Summary

At the Free Hospital for Women there have been twelve primary carcinomas of the Fallopian tube out of 3,878 primary malignant lesions of the female genital tract in the 90,611 admissions from 1903 to 1948, an incidence of 0.31 per cent of primary malignant tumors.

Vaginal discharge is the most common symptom. Sterility was associated in 27 per cent. Hydrops tubae profluens was not the characteristic symptom as held in the literature. Other common signs or symptoms are pain, tumor mass, menstrual irregularities, or postmenopausal bleeding.

Preoperative diagnosis is next to impossible. The routine use of the vaginal smear may prove to be a helpful adjunct.

There appears to be a fairly consistent correlation between histological grading and prognosis, the well differentiated papillary forms having a good prognosis, although the five-year survival of the entire series was 40 per cent.

Panhysterectomy, bilateral salpingo-oophorectomy, followed by postoperative radiation, is the treatment of choice.

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HABITUAL ABORTION: THE INCOMPETENT INTERNAL OS OF THE CERVIX*

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THE etiology of habitual abortion must include many predisposing and exciting causes since so many conditions need be fulfilled for a conceptus to reach maturity. The requisites for a normal male and female constitution as well as generative tracts for reproduction are multiple and complex. It is, therefore, readily understood when Litzenberg in Curtis' monograph on *Obstetrics and Gynecology* says, "Cases of repeated abortion belong preeminently under the heading: 'No Discoverable Cause.'" The appreciation of the multiplicity of causes will dispel the confusion of the problem of habitual abortion as discussed by Hunt. The search for the one elusive cause which will explain all abortions of this type will cease.

Currently, wheat germ oil and the hormones hold the therapeutic field. The tremendous amounts of wheat germ oil and its derivatives, and of the hormones (progesterone, thyroid, estrogens, anterior pituitary, and parathyroid) have not been successful in many instances as one might have anticipated since there has been no body deficiency of any of the given substances.

It is, therefore, with this full awareness of the multiplicity of etiological factors in habitual abortion that we present the subject of the incompetent internal os as one of the many causes of habitual abortion, but one that is often overlooked.

Our observations are based on personal cases and those of our colleagues at The Michael Reese Hospital.

In the standard textbooks of obstetrics and gynecology, as well as in the recent monographs, there is no mention of this condition of the cervix in the chapters on habitual abortions. The literature is also devoid of discussion or study of this condition as far as we are aware, particularly in the last twenty-five years, during which time our acquaintance with it has been fairly intimate. The only reference to this cervical condition has been made by N. Sproat Heaney by personal communication. In answer to my query about his experiences with this condition, he writes, "I never have published anything directly on the subject of incompetence of the internal os as a factor in habitual abortions. I have mentioned the subject, however, many times in discussions."

*Presented before the Chicago Gynecological Society, Oct. 15, 1948.

The etiology of the incompetent internal os may be a dilatation (probably overdilatation with resulting laceration), a curettage with too much zeal, especially through the anterior wall of the internal os, previous abortions followed by dilatation and by curettage, vaginal hysterotomy, or vaginal cesarean, rapid labors or cesarean section (lower uterine segment).

According to Heaney, "the greatest contributing factors, in my experience, to this condition are tearing of the cervix by labor or by instrumental dilatation and incomplete healing after vaginal cesarean section or vaginal hysterotomy. When doing either one of these procedures, I have emphasized sewing up the cervix with two layers of interrupted catgut, the first layer including the mucosa and about one-half the thickness of the cervix with the knots tied inside the cervical canal and the second layer completing the closure of the cervical incision. The use of a single through-and-through suture with subsequent necrosis is the chief factor in getting an incompetence of the internal os. The external os usually has a normal appearance."

Today, vaginal cesarean or hysterotomy is less commonly done but the same conditions may prevail after an abdominal lower uterine segment or cervical cesarean (laparotrachelotomy) where improper suturing or infection may result in incomplete healing. The degree of incompetency may vary so that habitual abortion may not always occur if the defect is slight, especially if the patient is restricted to the supine position for months until term is approached in order to prevent the herniation of the dependent bag of waters or presenting part through the partially open internal os.

Occasionally, the laceration of the cervix may extend down the entire length so that it may be visible at the external os. This type of trauma may follow forceps operations (Koff's case) and be the basis of repeated abortions until the defect is remedied. In these instances the laceration must extend from the external os up through the internal os when the head is dragged through an incompletely dilated cervix or through a cervix which has not been drawn up above the head when the cervix is imprisoned between the large engaged head and the symphysis pubis. An internal os laceration might be produced when the shoulders are forcibly pulled through an unsuspected constriction ring. Most of the defects of the internal os observed have been in the anterior wall rather than in the lateral wall where the long lacerations are usually found.

The pathology found is a defect in the internal os which is best detected during an abortion, when the finger introduced into the cervical canal finds a thin scar between the cervical canal and the bladder. After the bladder has been dissected off the cervix, the thin scar is especially evident and the defect may vary from 1 to 2 cm. in width and be 2 to 3 cm. in length. The associated childbirth injuries are retrodisplacement and descensus uteri, cystocele, and relaxed pelvic floor. The defect has been confused with upper cervical canal Nabothian cysts, when the cervix has been recognized as the seat of the pelvic pathology.

The symptoms of the incompetence of the internal os are chiefly those of habitual abortion and of the associated pathology. Examination usually reveals a normal-appearing external os of the cervix and only by exploration with uterine dressing forceps may one find the patent internal os. However, the defect is readily found after an abortion. The characteristics of an abortion due to an incompetent internal os are sudden rupture of the bag of waters followed by a rapid and relatively painless extrusion of the products of conception.

The diagnosis is made on the history of repeated abortions and finding the patent internal os.

From his experiences, Heaney further states, "This condition occurs frequently enough so that when an abortion is in progress or has apparently just completed itself, I routinely advise a dilatation and curettage so that in addition an immediate examination of the cervix for the presence of a weakened internal os for the softening and dilatation allow the suspicion of an imperfect internal os to be verified and repaired at that time. Later when involution has become complete and the tissues are again hard, repair is difficult because the tissues are inelastic and the sides of the defect are difficult to bring into good apposition."

The treatment is, of course, repair of the defect, most desirable immediately after an abortion. However, we have had no great difficulty in repairing the defects in nonpregnant patients. The bladder is dissected off the cervix after a transverse incision through the vaginal wall about 2 cm. above the external os. With the bladder retracted, the defect may require simple bringing together of the edges by interrupted No. 2 chromic catgut sutures (three or four) or the scar may be excised and the edges coapted with the interrupted sutures. The anterior portions of the cardinal ligaments may also be sutured into the midline of the cervix if a descensus uteri is present. The vaginal wall is sutured into place with interrupted No. 0 chromic catgut or if a cystocele is present it may be corrected at this time. It is interesting to note the change in the closure of the internal os before and after the repair. The postoperative course is usually uneventful. The prognosis is good, for all those whose defects were repaired and who subsequently became pregnant carried to term or near enough to have viable babies.

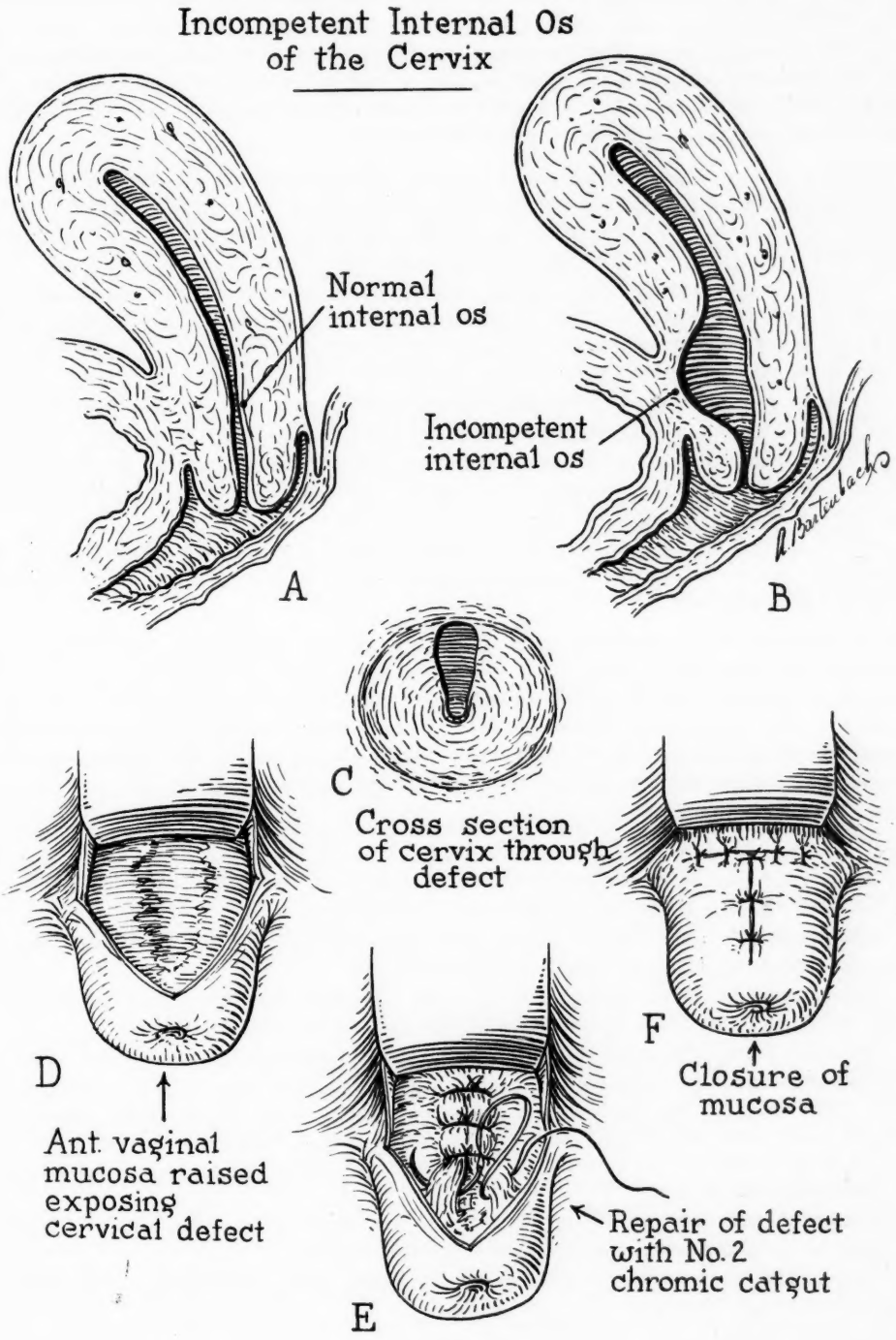
The case reports upon which this study is based are as follows:

CASE 1.—A. S., 31 years old, white, para 0, gravida iv, sought advice because of repeated abortions. She had been married six years and had had an induced abortion shortly thereafter. A year later, she became pregnant and had a miscarriage at the sixteenth week of her pregnancy. She had two similar experiences at yearly intervals. Her past history and menstrual history had nothing of significance except the above-noted episodes of habitual abortion. Physical examination showed a normal individual with the only significant finding being an incompetent internal os of the cervix. On Sept. 27, 1941, I performed a diagnostic curettage, excised scar tissue from the anterior wall of the cervicocorporeal junction and closed the wound with interrupted No. 2 chromic catgut sutures. The anterior portions of the cardinal ligaments were sutured to the anterior cervical wall. The patient made an uneventful recovery. She returned Oct. 2, 1942, pregnant sixteen weeks and, following an uneventful pregnancy up to the thirty-sixth week, she went into labor and delivered Feb. 9, 1943, by low forceps and episiotomy, a 5 pound, 8 ounce boy.

Her second pregnancy went to term and she delivered Jan. 17, 1945, spontaneously with episiotomy, a 7 pound, 1 ounce boy. Subsequent annual checkup examinations found no pathology.

CASE 2.—B. S., aged 32 years, white, gravida iii, para 0, came because of repeated miscarriages. She had had no previous illness or operation. She had had a spontaneous abortion (eighteen weeks) in 1941, another one of eighteen to twenty weeks in 1942, and a third one of twenty weeks in 1943. Wassermann test was negative, the blood count and urinalysis were normal. Physical examination revealed a normal individual except for the pelvic findings of an incompetent internal os on exploration with a uterine dressing forceps.

On May 25, 1945, under local anesthesia, a dilatation and curettage were performed and after dissection of the vaginal wall off the cervix, the thinned anterior wall of the cervix at the internal os was demonstrated. The edges of the cervix at this point were freshened and four interrupted No. 2 chromic catgut sutures were placed to obliterate the defect.


Incompetent Internal Os
of the Cervix
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Ant. vaginal
mucosa raised
exposing
cervical defect
E
Repair of defect
with No. 2
chromic catgut
F
Closure of
mucosa

Fig. 1.

The anterior portions of the cardinal ligaments were sutured into the anterior cervical wall followed by closure of the vaginal wall. The recovery was uneventful and the patient was discharged after five days.

She returned July 2, 1946, pregnant six weeks. Her pregnancy was normal and on Feb. 28, 1947, she was delivered by outlet forceps and episiotomy, of a female child weighing 6 pounds, 11 ounces, after a seven-hour labor. Postpartum examination (six weeks) found normal involution with normally closed internal os.

CASE 3.—A. A., aged 27 years, white, gravida ii, para 0, consulted us because of an eight weeks' pregnancy. The most significant historical information was a dilatation and curettage, and perineotomy for "smallness" of her female organs three years ago. One and one-half years later a spontaneous sixth months' miscarriage occurred.

Her physical condition was normal; blood count, normal, and the Wassermann test negative. She continued with this pregnancy for six months when suddenly she went into labor and delivered spontaneously a two-pound male child who died shortly thereafter. Postpartum examination revealed a defect in the internal os.

Twenty months later a dilatation and curettage, repair of the anterior cervical wall at the internal os, and multiple myomectomies (five small fibroids) were performed.

Six months after her operation, she returned with an eight weeks' pregnancy which continued to term and she delivered a normal boy weighing 5 pounds, 13 ounces. Subsequent postnatal examination found normal involution with a closed internal os.

Four years later, she returned with another pregnancy which terminated normally with the delivery of another boy weighing 6 pounds, 8 ounces. Involution was found to be normal at her postnatal visit.

CASE 4.—E. B., 24 years old, white, gravida iv, para 0, complained of right lower quadrant pain when nervous, six weeks' duration. She gave a history of four spontaneous abortions—first, ten weeks, followed by dilatation and curettage; second, fourteen weeks; third, fourteen weeks; and fourth, sixteen weeks. The last three abortions were not followed by dilatation and curettage. General examination found no pathology. Essential pelvic finding was a patent internal os. This patient did not return for therapy.

CASE 5.—R. D., aged 32 years, white, gravida ii, para i, came because of relative sterility. She had been married for eight and one-half years and had a 7-year-old girl. The labor was mild for twelve hours and then suddenly her contractions became very strong and frequent. Shortly thereafter the labor was terminated.

One year later she became pregnant and progressed to the fifth month when the bag of waters ruptured suddenly and she had a painless labor.

Her current menstrual history attracted our attention. She was six days late and her period continued in the form of spotting after the usual flow of four days.

Physical examination found a normal individual with normal blood count, with the following pelvic findings: a patent internal os and a right tender adnexal mass (small walnut size). The diagnosis was made of an incompetent internal os of the cervix with an unruptured right tubal pregnancy. A dilatation and curettage, with repair of the cervical defect, were done, followed by a posterior colpotomy with right salpingectomy for an unruptured ectopic pregnancy.

Eleven months later she returned pregnant and went to term, delivering a 6 pound, 14 ounce boy. Postnatal examination found normal involution.

She is now pregnant two years after the last time. Her pregnancy has been uneventful and she is due Sept. 10, 1948.

CASE 6.—I. J. (patient of Dr. A. Koff), 39 years old, white, gravida iii, para i, was first seen in 1940 with a history of a pregnancy in 1938, which was complicated by eclampsia. Forceps failed and finally a cesarean section was performed with the delivery of a 9 pound, 4 ounce infant, who died five days later. Her next pregnancy in June, 1940, terminated spon-

taneously at three months. This was repeated in December, 1941. In April, 1942, an Emmet repair was done of the cervical laceration which apparently had been incurred during the failed forceps attempt in 1938.

Following the cervical repair the patient became pregnant and was carried to term on two occasions, Feb. 25, 1943, and Feb. 27, 1945. Elective laparotrachelotomy was done at term with delivery of two normal children. A myomectomy and tubal ligation were done after the last section.

Her postpartum course was uneventful.

CASE 7.—J. M. (patient of Dr. A. Tulsky), 29 years old, white, married six years, had been pregnant eight times, but had delivered no living child. Her first abortion occurred in October, 1941, the fetus was 10 to 12 weeks old. One month prior to the mishap she had intermittent bleeding which later became continuous with loss of the fetus.

She conceived again in January, 1942, and in May, 1942, she started to bleed and lost the fetus. Intermittent bleeding followed and a dilatation and curettage were done in July, 1942.

Her third pregnancy started in November, 1942. She received daily injections of Lupo-lutin. In January, 1943, she spotted and was confined to bed. In March, 1943, she felt life for one week and suddenly lost the fetus. Several days after the miscarriage she had a dilatation and curettage to ensure that the "afterbirth" was out.

In November, 1943, she began her fourth pregnancy, recevied one unit of progesterone daily during this pregnancy. She felt life in March, 1944, for one week; suddenly the bag of waters broke spontaneously and the fetus followed immediately. No dilatation and curettage were performed.

The fifth pregnancy began in January, 1945. During this time she was given 5 mg. progesterone intramuscularly daily plus thyroid extract. She felt life for one month when the bag of water ruptured spontaneously and the fetus was delivered four hours later (July, 1945). No dilatation and curettage were performed.

The sixth pregnancy was characterized by two months' amenorrhea followed by severe hemorrhage lasting three days. She was hospitalized and had a dilatation and curettage and blood transfusion. She received Theelol and vitamins and blood transfusions. Pathological report revealed a pregnancy (January, 1946).

The seventh pregnancy began shortly thereafter (February, 1946). She felt life for two weeks in June, 1946, when the bag of waters ruptured spontaneously and a macerated fetus was delivered five days later with instruments. No dilatation and curettage were performed. She had a left femoral thrombophlebitis of mild degree.

The above history came as an abstract from a clinic in Wisconsin.

The patient came to the Michael Reese Hospital Endocrine Clinic Aug. 4, 1947, with a six to eight weeks' gestation, and was observed for one week. The last menstrual period was June 6, 1947. Physical examination revealed a white woman, 5 feet, 8½ inches tall, weighing 150 pounds. Blood pressure 118/60. Blood work-up and chemistry normal. Basal metabolism rate was minus eight per cent. She was given intramuscular progesterone with normal pregnandiol recoveries.

She was readmitted during the fourth month of pregnancy (Oct. 6, 1947) to be observed while on bed rest and progesterone therapy. She received 2,400 mg. of progesterone from October 6 to about November 3. She felt life on October 10, and was very apprehensive about every symptom such as gaseous distentions. She was on sedatives, continued bed rest, and progesterone in high doses. On Nov. 3, 1947, she began to have some mild contractions for about three hours, the bag of waters ruptured, and her contractions became severe associated with moderately severe bleeding. An aseptic vaginal examination revealed a placenta previa lateralis in a partially dilated cervix (3 to 4 centimeters). Both feet were brought down, followed by delivery of the head shortly thereafter. The placenta was delivered by ring forceps.

Several hours later the patient was prepared for operation. Under ethylene anesthesia, examination found a 2 cm. dilated cervix with a defect at the internal os about 1 cm. in breadth at 12 o'clock (Dr. A. Tulsky). A transverse incision was made in the vaginal mucosa near its reflection off the cervix. The bladder was bluntly dissected back and the cervix exposed. Three sutures of No. 2 chromic catgut were placed in the anterior cervical wall bringing the edges of the defect at the internal os together. The vaginal mucosa was sutured into its former site. Patient made an uneventful recovery and was discharged Nov. 10, 1947.

In answer to a recent inquiry, the Endocrine Clinic was informed that the patient had another pregnancy last spring which terminated in eight weeks. The villi showed hyaline degeneration.*

Discussion

An analysis of the case reports reveals the overdilatation of the cervix in patient A. S., producing the incompetent internal os and resulting in three abortions. Repair of the defect of the cervix was followed by two normal pregnancies and deliveries. The same conclusion may be drawn about patients B. S. and A. A. History and findings of patient E. B. were suggestive but could not be substantiated. From the interesting history of patient R. D., one may deduce that a spontaneous rupture occurred. Such instances have been known to occur and cause serious and even fatal postpartum hemorrhage due to rupture of the uterus caused by violent uterine contractions followed by rapid labor. Patient I. J. had a traumatic obstetrical history to account for her ruptured cervix and internal os. The amazing history of J. M. with her multiple pregnancies and most thorough endocrine study certainly is a classic instance of an anatomical defect. However, her subsequent episode speaks for more than one cause for her habitual abortions.

Conclusions

1. Although endocrine factors play a frequent and important part in the etiology of habitual abortion, anatomical abnormalities are often overlooked.
2. The incompetent internal os of the cervix is so often not recognized because it is not obvious.
3. This condition, if sought, is easily recognized, remedied, and has a good prognosis.

Discussion

DR. D. N. DANFORTH.—One of the most fascinating aspects of obstetrics is the fact that the uterus is almost completely inaccessible in so far as the direct study of its dynamics is concerned. If it were possible to observe the uterus in action we should be deprived of a huge and dramatic literature dealing with interpretations based upon isolated observations. So it is in habitual abortion. If, in the cases to which the authors refer, it were possible to see the internal os in a state of incompetency, and to see the membranes dipping into the cervix when they should be confined to the corpus, the matter would be settled. But since we cannot actually observe these phenomena, the question must be approached indirectly.

The thesis which has been presented rests upon three major tenets. The first of these holds that incompetency of the internal os per se may be the cause of abortion, the implication being that under normal circumstances it is the internal os which constitutes the barrier confining the products of conception within the uterus. At the present time the preponderance of evidence appears to indicate that it is the cervix, and not the internal os,

*_Note._—Case 7. J. M. Delivered of first viable baby on April 28, 1949, by cesarean section because of placenta previa. Baby weighed 4 pounds, 4 ounces, the only living child from her ten pregnancies.

which serves this function, as witness for example the abortion which inevitably follows high amputation of the cervix. Since such amputations are invariably made below the level of the internal os, the cervix itself, and not the internal os, would appear to be the critical structure. Furthermore, there is evidence, which I consider good, that the so-called internal os (i.e., the anatomical internal os of Aschoff) in normal pregnancy becomes, in fact, so completely incompetent as to lose its identity altogether. For these reasons, I believe that the burden of proof rests upon those who would incriminate some structure other than the cervix proper.

The second tenet holds that this condition of incompetency is capable of clinical diagnosis by the techniques which have been mentioned. I am not prepared to discuss this point at length since I have not before had occasion to search for such a defect. However, the thought occurs to me that careful Lipiodol studies employing nonopaque instruments might be of great value in demonstrating such a lesion. Also, I should like to take exception to Dr. Heaney's advice that routine curettage should be done in incomplete and complete abortion in order that incompetency of the internal os may be tested. It has been shown beyond question that between nine and sixteen weeks' gestation, the structure known as the internal os in the nonpregnant uterus is obliterated by reason of the dilatation or unfolding of the isthmic segment. It would appear unreasonable after curettage, and particularly where this dilatation has already occurred, for the internal os to regain immediately sufficient integrity that one could make a judgment as to competency or incompetency.

Third, it is suggested that this lesion may be repaired surgically by plication of the anterior cervical wall. Of the cases presented, three do not answer the common definition of habitual abortion, namely, a condition in which a woman has had three or more consecutive spontaneous abortions. In a fourth case the lesion was diagnosed but was not treated and there was no follow-up. In one case the lesion was diagnosed and operated upon, this being followed by another spontaneous abortion. Thus, in a series of three bona fide cases of habitual abortion which were studied in accordance with the thesis presented there were two successful results and one failure. This series seems too small to act as material substantiation of the theory which is presented. Also, in the two successful cases, no mention is made of any other therapy, as for example, thyroid extract, stilbestrol, progesterone, bed rest at the time of the expected menses, etc. The data would be more suggestive if it could be stated that the management of these two patients was precisely that of an uncomplicated pregnancy.

In conclusion, may I say that although I believe the theory is of interest, the evidence supporting it is incomplete. Also, in assessing any results in the treatment of habitual abortion, one must remember that with no treatment whatsoever, it is variously estimated that between 12 and 27 per cent of patients will deliver viable babies. With judicious attention to certain simple measures the salvage should be significantly higher.

DR. EDWARD ALLEN.—This report by Dr. Lash and the discussion by Dr. Danforth bring up again a consideration of the histology and function of the cervix during pregnancy. As Dr. Lash has stated, the causes of habitual abortion are probably so varied and many of them so obscure that it is frequently impossible or at least hazardous to be certain about the relative importance of the various factors even when a definite anatomical or histological lesion can be demonstrated.

Malpas has calculated that a woman who has had three or more successive miscarriages has about a 27 per cent chance of going to term in her fourth pregnancy. He does not mention cervical lesions specifically, but reports that five out of nine of his sequential abortive patients who had had marked cervical trauma delivered at term in a subsequent pregnancy.

It is quite probable that several factors predisposing to abortion may be present in the same patient, as Dr. Lash has indicated in his discussion of the last case in this series.

I have no doubt in my own mind that defects in the cervix may occasionally cause abortion and/or premature labor. In former days when we did many amputations for endocervicitis, I was so impressed with the speed and ease with which a considerable number of

these patients lost their pregnancies before viability, or had almost a painless labor, that I suggested that amputation might be preferred in certain selected cases as a part of other procedures to shorten and make less painful subsequent labors. This suggestion was backed by youthful enthusiasm and inexperience.

Taussig does not mention anterior cervical lesions specifically but says that obstetric trauma to the pelvic floor supports, particularly those that extend into the parametrium, lead to abortion. He quotes Jahuhe as reporting an increased incidence of abortion after vaginal cesarean section and Leonard reports an increase after amputation of the cervix.

However, I can remember quite vividly at least four patients who were never able to carry their pregnancies to viability after their operative procedure. Three had amputation of the cervix, the other a traumatic dilatation of the cervix with a Goodell cervical dilator. An unsuccessful cervical repair, following three early abortions, was done on this last patient. Two subsequent pregnancies again ended in painless miscarriages at ten and fifteen weeks' gestation. Either the repair was inadequate, or the lesion had nothing to do with the miscarriage.

Just how long or thick does the connective tissue "puckering string" of the cervix need to be before it will hold a pregnancy to term? If the lesion produced by amputation in the first three patients was the causative factor in miscarriage, it was due to injury to the lower portion or external os of the cervix. It is conceivable that we cut away all of the holding connective tissue that Dr. Danforth has previously discussed in his paper on "The Fibrous Nature of the Human Cervix." We may have left only the musculoconnective tissue union which was relatively incompetent as a holding mechanism against Braxton Hicks' contractions after the fifteenth week of gestation.

We have encountered habitual abortion in two additional patients who elsewhere had previously been subjected to an extensive conization. We felt that the small amount of cervical tissue left was probably a factor in the early miscarriages.

We have not been so fortunate, as has Dr. Lash, in repair of lesions of the anterior portion of the cervix following vaginal cesarean section or hysterotomy. In the repair of two of these patients who subsequently developed habitual abortion, the cervix did not heal well. In our experience, lesions through the midline of the anterior lip of the cervix do not heal as well as do those in other quadrants. This may be due to the relative avascularity of this region or its attachments to the anterior septum. Most of the lesions described in Dr. Lash's paper occurred in this anterior region and I should like to ask Dr. Lash if the lesion was anterior also in Cases 5 and 6.

DR. LASH (Closing).—I tried to bring out that this was a clinical study. It is difficult to evaluate therapy by clinical results, especially in a condition in which there may be many etiological factors. I am sorry I did not have any uteri in any one of these instances to study anatomically to determine just where that defect was, whether it was in the corpus proper or down in the cervix. I purposely called attention to the internal os because it is with that region that I am concerned. A finer definition of the internal os is of academic interest. This sort of study does not lend itself to statistical conclusions. But even a small number of cases may give sufficient information for one to draw conclusions. We noted small myomas in one case. Clinically I did not think they played much of a part in causing the abortion, since they were all marble sized and subserous. There were many other instances of slight defects in the internal os, where the woman was put to bed without any repair and allowed to go to term. It is only in the more extensive ones where there is a good bit of defect that repair is necessary. Maybe I was overenthusiastic when I saw a woman with only two spontaneous abortions which I considered habitual and did not follow the textbook definition, but the condition was too obvious to be overlooked. The interesting observation is that these abortions occurred in the second trimester and not in the first when they might be of hormonal origin. When they occur in the middle trimester they are more likely to be of mechanical origin.

A REVIEW OF CESAREAN SECTION AT SLOANE HOSPITAL FOR WOMEN, 1942-1947*

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ONE of the most important changes that is taking place in obstetric practice is indicated by the trend of substituting the cesarean section operation for the more formidable, traumatizing vaginal delivery. Obviously this change is being effected only in proportion to the increasing safety of the operation. Recently, with the advent of positive and efficient means of treating infection and shock, the cesarean section mortality rate has been materially lowered. At the Sloane Hospital, for example, the last death directly attributable to the operation occurred in September, 1941. During the seven years since then we have done 1,266 cesarean sections with only one death, which in no way was related to the operation. It seems that such uniformly good results make it worth while to report our more recent experiences with this operation. The observations made in the course of studying the first 1,000 cases which were done after September, 1941, are the basis for this paper.

The Cesarean Section Rate

1. *Gross Rate.*—

During the period covered by this study, 17,226 patients were delivered with a cesarean section rate of 5.80 per cent. The rate on the ward service was 4.47 per cent and on the private service was 7.72 per cent. The difference in the ward and private cesarean section rates is worth comment. The higher rate on the private service has been reported by other clinics, and to a greater or lesser degree seems to be fairly general practice. In reviewing the cases it is obvious that on the private service all the factors which reflect on the desirability of obtaining a living child are focused in the attention of the physician and as a result great emphasis in this direction, which sometimes is unduly slanted, becomes the keynote in the management of the patient. The same staff dealing with the ward problem is more likely to follow the means of standard procedure. It appears that this more complete individualization of the private patient results in greater latitude within the limits of acceptable indications and more cesareans are done in the interest of the child or done rather to avoid even minor risks to the child. This policy often has the effect of unnecessarily increasing the rate.

2. *Factors Affecting Rate.*—

Representative figures for the incidence of cesarean section in the Eastern half of the country are given in Table I. Our rate is a little less than one per cent above this average. These comparative figures are shown to bring out the point that considerable variation in the cesarean section rate exists. Is it fair to ask ourselves whether our rate is too high? Are there any criteria by which we can establish a proper cesarean section rate?

*Presented at a meeting of the New York Obstetrical Society, Oct. 12, 1948.

Strict comparisons between clinics are not justifiable because too many variables are concerned in the accounting. Only when the deviations from the average are excessively high or low can we critically indict a given institution for either too radical or conservative approach to their labor problems.

When the reasons for the variations in the cesarean section incidence are carefully appraised it will be noted that at least five variables enter the calculation. The differences in rates between ward and private practice have been already mentioned. It follows, therefore, that the partition of ward and private patients in a given service will have an effect on the total incidence of the operation. Another important variable is the number of applicants from which the patients are chosen. Our antepartum clinic interviewed from fifteen to twenty-five applicants daily during the course of this study, from whom eight or less were accepted. The selections were influenced to a great extent by the presenting and expected obstetric complications. This degree of screening definitely increases the incidence of cesarean sections. A third factor is concerned with the genetic nature of the population from which patients are chosen. It has been shown and our own experience indicates that there is a higher incidence of obstetric problems among the Negroes. A larger proportion of these people is found in the cities of the South and East than in the rest of the country. Then there is a fourth factor, the standing of a given hospital in a community, especially in the larger cities where various obstetric services are in a sense largely competitive in so far as prestige is concerned. Finally, there is the obstetrical staff itself which can vary so much in policy, organization, teaching responsibilities, training, and tradition. It is this last-mentioned multiple factor that is usually considered to be most important in determining the incidence of the operation, but, as pointed out, there are so many others that it is practically impossible to compare the rate of one institution with that of another.

TABLE I. CESAREAN SECTION RATES

New Haven Hospital	5.9%
Margaret Hague	2.6%
Chicago Lying-in	5.5%
New York-Cornell	2.1%
Boston City Hospital	4.2%
Kansas City	7.1%
Johns Hopkins Hospital	5.5%
Cleveland Maternity	6.1%
Philadelphia Lying-In	5.8%
Sloane Hospital	5.8%
Average	4.9%

The matter of the cesarean section rate will be of considerable interest in the next five or ten years, for there appears now to be a definite tendency to broaden the indications. The greater safety of the operation makes this obvious. Once a trend is started it is often carried too far. It will be of some value to know, then, by what criteria the probable increasing rates of the future shall be assessed. For the reasons mentioned we cannot use the lowest reported rates as the ideal because this might not only involve a comparison of two entirely different cross sections of obstetric practice but it may also be true that the service with the lowest rate is not necessarily practicing the best obstetrics within the limits of their own material. It is obvious therefore that a given rate can be critically evaluated only in terms of the results obtained in the institution of origin and it will not be comparable necessarily with that of another.

3. *Evaluation of the Cesarean Section Rate.—*

Cesarean sections are done in the main to avoid trauma to the mother and child which results from complicated vaginal deliveries. For this reason we should be able to strike some reciprocal relationship between the number of cesarean sections on the one hand and the incidence of trauma on the other. An upward trend of the cesarean section rate in any service is justifiable only if it can be shown, first, that the increased number of operations does not increase the maternal mortality and, second, if it is consistent with a fall in the traumatic vaginal operations and the obstetrically preventible fetal deaths.

The maternal mortality is the first term in our formula for it is not in the best interests of the patient to broaden the scope of the operation until it is at least as safe as the more difficult vaginal operations. Until that time, we are obliged within reason to lean toward the latter in spite of their traumatic possibilities. There is no way by which we can evaluate maternal lives in terms of anything else. However, when these rates have become equalized, there is justification in broadening the indications for the cesarean operation if it can then be shown to reduce further fetal and maternal trauma.

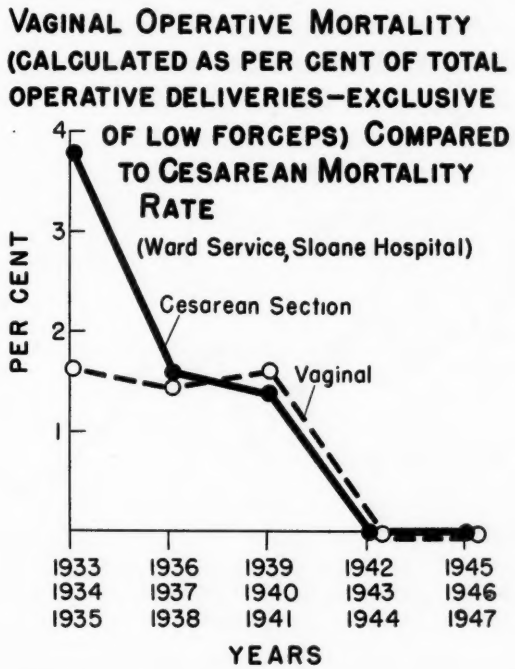

Fig. 1.

First, therefore, we should compare the vaginal operative and cesarean section mortality rates (Fig. 1). It is apparent from this that there was justification in the attitude that prevailed fifteen or more years ago when the cesarean section rate was maintained at the lowest possible level for, generally, it was safer for the mother to be delivered by vaginal operation. For the past nine years, however, our experience shows that it is not any more hazardous to the mother to deliver her by cesarean section than by vaginal operation, low forceps excluded. This has permitted greater latitude in the use of the cesarean operation and it becomes necessary to justify or refute our new position.

As already indicated, the cesarean section rate should be inversely proportional to the incidence of fetal and maternal trauma, using the latter term in its broadest sense. How is this trauma to be calculated? At the Sloane Hospital the midforceps delivery rate provides a good index of trauma because the version and high forceps operations are rarely employed. While not all midforceps deliveries are difficult, it is true that injury to both mother and fetus occurs frequently with this operation. To show this, a comparison of the incidence of midforceps with term birth injuries taken from our autopsy files, which cover practically all fetal deaths, shows a striking direct proportional relationship (Fig. 2). When it is realized too that the maternal

Fig. 2.

pelvic supporting structures must be damaged to the same degree, it follows that the ideal to strive for is the elimination of this operation as much as possible. It may well be predicted here that the difficult, traumatic midforceps operations will be relegated to the obsolete procedures along with craniotomy, high forceps, version, the bags and bougies. It is obvious that the operation is being eliminated slowly, for in Fig. 3 it is noted that the midforceps and cesarean sections have virtually changed their respective positions of usefulness within the past twenty-seven years. If the trend shown here were to continue in this way the midforceps on our service could reach a theoretical zero with a cesarean section incidence of 6.5 per cent. From a practical point of view this is not entirely desirable since a certain number of the easier midforceps deliveries will always be done. For this reason a cesarean section rate of 6 per cent should be adequate, in our own case, to eliminate maternal and fetal trauma caused by difficult vaginal operations.

In addition to the practical elimination of maternal pelvic and fetal injury due to operative vaginal delivery, the scope of the operation has been broadened to save the lives of infants that succumb to the accidents and complications of labor such as placenta previa, accidental hemorrhage, cord complications, malpresentations, prolonged labor with infection of the sac, etc. These deaths, which in a sense are preventible, fall into three major categories, namley, birth trauma, anoxia, and infection. Since it is often difficult to be certain of the cause of death in such cases, unless the fetus has been carefully studied post mortem, it is better practice to calculate the preventible fetal death rate by subtracting the obvious nonpreventible group from the total fetal deaths. The nonpreventible group includes the immature child, the congenitally

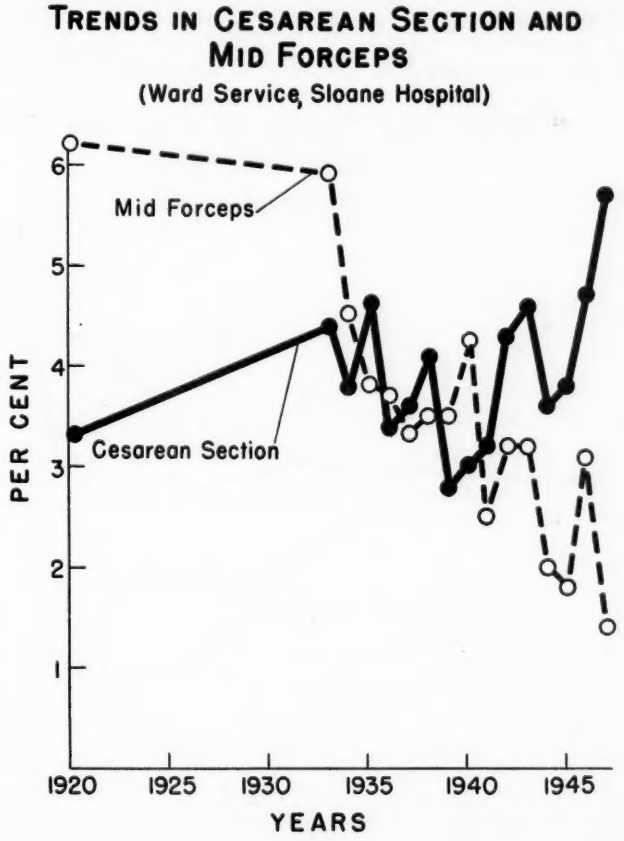

Fig. 3.

malformed fetus, and those that die in utero before labor. In Fig. 4 the cesarean section rate has been compared to the theoretically preventible fetal death rate calculated in this way. It is apparent that a considerable decrease in fetal deaths of this type occurred between 1927 and 1941 with no appreciable change in the cesarean section rate. During this period, as noted previously, the midforceps rate was lowered considerably and accounts for much of this saving of fetal lives. We believe that this was accomplished in the main by two factors: first, by the inauguration of the residency system, which came into full operation in 1927, and, second, by the extensive use of radiological techniques in the study of labor problems, permitting greater accuracy in the prognosis of labor. More recently these preventible deaths have been decreased even more and this we believe is the result of a more liberal cesarean

section policy. It would seem that a practical cesarean section rate theoretically should be high enough to reduce the preventible fetal deaths calculated in this way to one per cent or lower.

In this series of cesarean sections covering a period of about six years there has been an increasing rate for both ward and private services. To assess these rising rates according to this principle of reciprocal relationships between cesarean sections on the one hand and trauma on the other, the cesarean section rate, midforceps rate, and preventible infant mortality were calculated for both services. The ward data (Fig. 5) show that the rising cesarean section rate is associated with a reciprocal fall in both the obstetrically preventible fetal deaths and traumatic vaginal deliveries and is therefore justifiable. The increasing rate on the private service (Fig. 6) on the other hand cannot be supported. Assuming that the nature of the private practice has not materially changed, a rate between 6 and 7 per cent instead of 9 per cent for the past two years would give the present results.

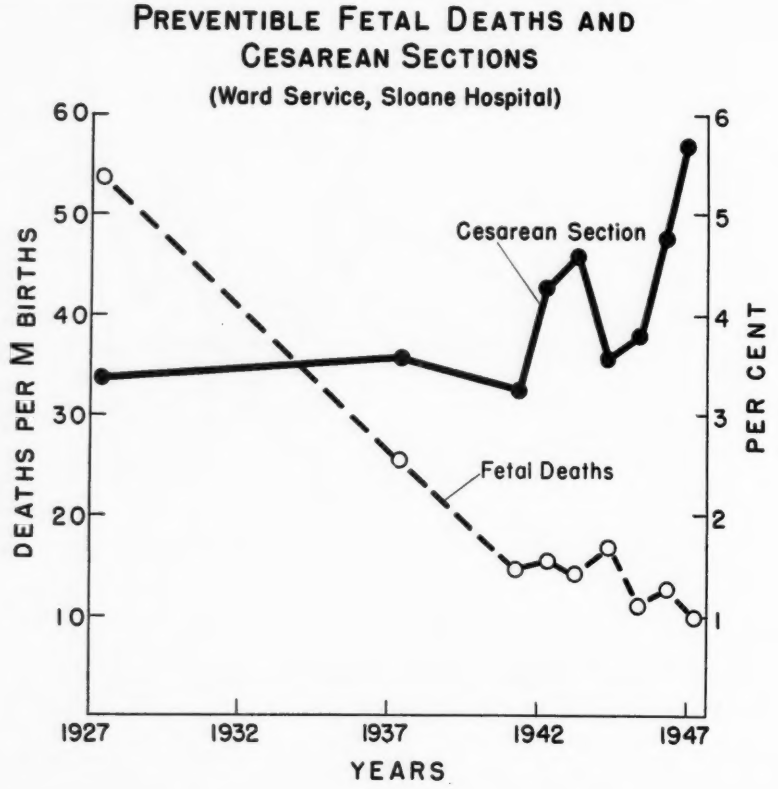

Fig. 4.

As a working formula for an obstetric service that deals with an abnormal group a cesarean section rate between 5 and 6 per cent with a maternal mortality of 0.1 per cent and a preventible term fetal loss of 1 per cent is suggested.

Racial and Age Factors in Cesarean Section

Both the age and race of the patient are significant in their effect on the cesarean section rate. In this series the operation was done in 5.8 per cent of the total Negro group that was delivered during the course of the study, as compared to 3.2 per cent of the white patients. This greater proportion of

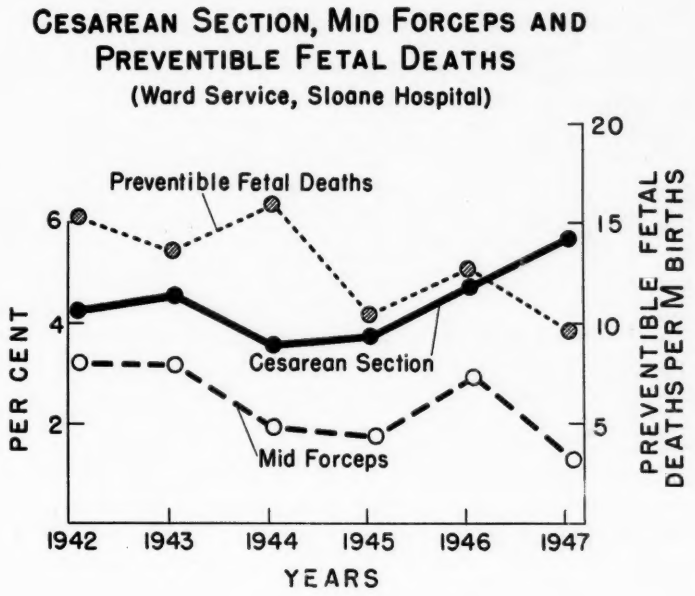
CESAREAN SECTION, MID FORCEPS AND
PREVENTIBLE FETAL DEATHS
(Ward Service, Sloane Hospital)
Preventible Fetal Deaths
Cesarean Section
Mid Forceps
PER CENT
PREVENTIBLE FETAL DEATHS PER M BIRTHS
YEARS
1942
1943
1944
1945
1946
1947
2
4
6
5
10
15
20

Fig. 5.

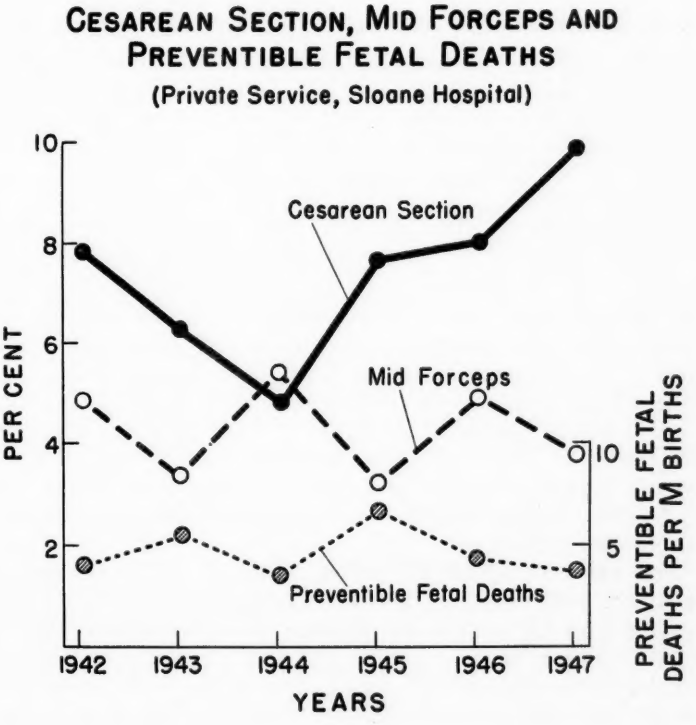
CESAREAN SECTION, MID FORCEPS AND
PREVENTIBLE FETAL DEATHS
(Private Service, Sloane Hospital)
Cesarean Section
Mid Forceps
Preventible Fetal Deaths
PER CENT
PREVENTIBLE FETAL DEATHS PER M BIRTHS
YEARS
1942
1943
1944
1945
1946
1947
2
4
6
8
10
5
10

Fig. 6.

cesarean sections done among the Negroes is mainly a measure of the increased incidence of cephalopelvic disproportion. Since the Negro group on our ward service has steadily risen from 18.7 per cent at the beginning of this study to 40.4 per cent at its close, this becomes one of the factors which partially accounts for the rising rate of the operation.

The incidence of cesarean section has been calculated at various age levels for all delivered patients. For both multiparas, and primiparas the rate increases with age. While this rise is slow in the multipara, it is very striking in the primipara after age thirty-five. For the primipara who is between 35 and 40 years old the cesarean rate is 37 per cent; when she is 40 years old or more the rate becomes 49 per cent. These observations show how often the indications for the operation are considerably more subtle than is indicated in the record, for while "elderly primipara" appeared five times as a stated primary indication and ten times as a secondary indication, it is apparent that age of itself, especially in the primipara, is a more important factor in the election of the operation than we realize. Many of these elderly primiparas present their indications at a minimal level and tests of labor are usually inadequate. However this may be, it is difficult to be adversely critical of this practice especially since in the past 14 years the gross fetal mortality rate for this older group is 2.8 per cent as compared to 4.3 per cent for the primiparas under 40 years ofage. The high cesarean section rate therefore seems to have its compensations in saving more babies in a group of women to whom a fetal loss is often an irreparable tragedy.

Indications

As in all studies of this type, cephalopelvic disproportion was the chief factor and it occurred in 539 cases. Of these, 319 occurred in women having their first section and 220 in the multiple sections. Thus it is seen that over half (53.9 per cent) of the operations are done for cephalopelvic disproportion—an incidence of 48.4 per cent among all primary sections, of 64.3 per cent for the multiple sections, and 2.6 per cent of the total delivered patients.

The criteria by which these cases are selected cannot be detailed here. It may be stated that, according to the method which will soon be published by Steer of our department, all patients with a questionable pelvis are divided into three groups according to the ratio between head size and inlet capacity. The groups are: (1) absolute disproportion, (2) borderline, (3) adequate. The capacity of the mid- and lower pelvis as visualized in the precision stereoscope may alter the prognosis based on this head-inlet ratio and occasionally becomes the deciding factor in spite of an adequate inlet. The borderline group represents most of the cases so studied and after a carefully conducted trial of labor, a majority of these deliver vaginally. Trial labor was allowed in 54 per cent of the primary sections that were done for disproportion. As already indicated there is a slowly increasing number of operations done for contracted pelvis with a corresponding decrease in the number of operative vaginal deliveries.

In 121 cases the operations were done because of a previous cesarean section in spite of an adequate pelvis. This indication—or the large number in this group—may well be contested in some quarters. It is true that in general we adhere to the policy of repeat sections after the initial operation, but not all of them are treated in this way. The patients are carefully examined when near term, an x-ray examination is made, and if all the factors making for an easy labor are present in a patient whose previous postoperative course was afebrile, delivery from below is permitted. Since we have not indexed the vaginal deliveries following cesarean section it is not possible to give this

figure readily, but it can be stated that most of the patients in this class are sectioned. A factor that bears on this point is that many of the primary cesarean sections in this group were done in other hospitals. The staff somehow seems less inclined to allow vaginal delivery in these outside cases than in those for which we were initially responsible. This may have some bearing on the fact that this group which constitutes 12 per cent of our cesarean sections falls into a class that theoretically could have delivered vaginally if we had trusted the integrity of their uterine scars. Any adverse criticism to this policy should take cognizance of the increasing safety of the elective section which gives us less and less justification for taking the risk of a ruptured uterus when we allow these patients to attempt to deliver themselves.

Placenta previa in third rank was the primary indication in 67 cases and in an additional 9 cases it was a secondary factor. Fifteen years ago 20 per cent of the cases of placenta previa in our clinic were treated by cesarean section. Since that time there has been a steady rise so that in the past five years that figure has reached 69 per cent. The indications for cesarean section for this condition seem to have been simplified and broadened to include any case in which there is active bleeding which cannot be controlled by simple vaginal procedures.

Uterine inertia and cervical dystocia together accounted for 71 cases and appeared as additional factors in another sixteen. The pelvic capacity in these cases was essentially adequate. Of interest in the change that has taken place in the management of this group in more recent years is the practical elimination of manual dilatation of the cervix followed by forceps delivery. This procedure was formerly considered preferable to cesarean section in view of the adequate pelvis.

Fibromyoma was the primary indication in 40 cases and was present as a secondary factor in 15 others. This figure must be interpreted in the light of the total incidence of fibromyoma associated with pregnancy which is 3.9 per cent in our clinic group. In most of the cases the operation was done when the tumors were large, irrespective of their location in relation to the pelvic brim. In 23 cases either because of the patient's age or the size and multiplicity of the tumors, hysterectomies were done. In an additional 34 patients myomectomies were performed. Fibroids and uterine inertia were combined in only three cases. However, since most patients with large fibroids were sectioned electively, this does not indicate to what extent distortion of the uterus by large tumors might interfere with the establishment of efficient uterine contractions.

Pre-eclampsia was given as the primary indication in 27 cases and in an additional 14 it was an accompanying condition. The trend here is slightly upward. There is a tendency now to do cesarean sections earlier in the non-inducible cases that do not respond satisfactorily to medical treatment. There were no cases of eclampsia.

In 24 cases the operation was done because of malpresentation. These were breech 12; transverse 8; face 2; compound 2; and brow 1.

Accidental hemorrhage, eighth in order, was a factor in 18 cases. Calculating the incidence of cesarean section for this condition in the past 15 years, including all types, shows a slow, upward trend which is not as striking as it appears in placenta previa. A breakdown of our cases into groups of varying severity would be necessary to appraise this trend accurately.

It is noted that in 5 cases the indication is given as expected erythroblastosis. These cases appeared earlier in the study. With increasing experience it seems that cesarean section, per se, offers very little advantage to the erythroblastotic fetus.

Rheumatic heart disease was the primary indication in only two cases. The trend in this condition has been downward. The policy is to allow more and more of these patients to deliver vaginally; in fact, cesarean section becomes a consideration only when the pelvis is abnormal or there are other complications of labor.

As additional causes the following are enumerated without comment: previous difficult delivery 12; previous plastic repair 11; fetal distress and cord complications 9; hypertensive vascular disease 6; obstructive ovarian tumor 4; previously unexplained stillbirth 4; previous myomectomy 4; genital anomalies 3; cicatrix of cervix 3; diabetes 2; carcinoma of cervix 2; retroplacental tumor 2; contraction ring 2; miscellaneous 17.

Complications

Fetal.—

It has been shown repeatedly that the infant mortality in cesarean section is higher than in the total group of delivered patients. This uncorrected figure has been sometimes erroneously pointed out as evidence of the fact that the risk to the child in cesarean section is great and that the operation offers a false sense of security for fetal survival. That this is not so is obvious, for when the causes of the 37 deaths are studied (Table II) it is noted that most of them are inherent in the maternal complication for which the operation was performed. In spite of this the gross fetal mortality rate of 3.7 per cent for the entire series compares favorably with the gross vaginal delivery mortality rate of 3.3 per cent for the same period.

TABLE II. INFANT MORTALITY. 37 CASES, 3.7%

NO.	MATERNAL CAUSES	FETAL CAUSES	TERM	PREM	STILL-BIRTH	NEONATAL DEATH
11	Accidental hemorrhage	Anoxia 8 Prematurity 3	2	9	8	3
10	Placenta previa	Anoxia 1 Macterated 1 Prematurity 8	1	9	2	8
4	Congenital defect		4	0	2	2
4	Toxemia	Prematurity 4	0	4	0	4
*4	Early interference	Prematurity 4	0	4	0	4
2	Not known	Antepartum death cause unknown	2	0	2	0
1	Rh incompatibility	Erythroblastosis	1	0	1	0
1	Vascular collapse Spinal anesthesia	Anoxia	1	0	1	0

*1. Error in date. 2. Premature labor in secondary section. 3. History of repeated stillbirths. 4. Carcinoma of rectum.

The operation itself could be indicted as a factor in five fetal deaths. In four the operation was done too early and in one of these there was no alternative because the operation was done as a preliminary step in a radical operation for carcinoma of the rectum. Of the three preventible premature deaths, a secondary section was done too early in one because the "expected date of delivery" was taken too literally; in another the secondary section was done early because the patient went into premature labor, and in a third the patient, who gave a history of repeated unexplained death in utero at term, was sectioned early in order to avoid the same unhappy ending, but the child died because he was immature. The fifth and most striking preventible fetal death occurred when the mother went into vascular collapse following spinal anesthesia. Although she responded to therapy, the baby in the meanwhile died of anoxia.

In the remaining 32 cases the deaths were not related to the cesarean section. The fetus was either dead before operation or died of congenital anomalies in seven. Twenty-five others died of anoxia or immaturity resulting from maternal complications which made the operation necessary.

Accidental hemorrhage accounted for the largest number of this latter group. Since this condition was an indication for 26 of the cesarean sections, the fetal mortality for this complication, 42 per cent, remains high even for those cases treated in this way.

Placenta previa accounted for 10 deaths. With 79 sections done for this complication the fetal mortality rate was 12.7 per cent. While the babies of the mothers with accidental hemorrhage died primarily of anoxia and were stillborn, the majority of the placenta previa babies were born alive and died of immaturity. A study of these cases seemed to indicate that frequently the operation might have been postponed because of the small size of the child. Supportive therapy and rest, if followed by cessation of bleeding, might have prolonged the pregnancy for several weeks with considerable improvement in the outlook for the child. There should be no risk to the mother in these cases if she is kept under close observation.

Toxemia of pregnancy accounted for 4 of the fetal deaths—all the result of prematurity. The toxemic patient often presents a difficult decision—that of electing the proper time to interfere. While the outcome of these 4 cases would suggest too early interference, on the other side there are the arguments that the operations were done to avoid the effects of prolonged toxemia and further that the babies might well have died in utero in any event.

Maternal.—

Although there were no maternal deaths that were attributable to the operation it is impressive to observe the list of complications in Table III. While in the main the operation has become safe, 107 patients presented some form of puerperal infection of variable extent. Although many of these were minor in degree it is indeed a tribute to the value of penicillin and the sulfonamides which were used in 74.8 per cent of the entire series, that not a single one of them was fatal.

TABLE III. COMPLICATIONS

Infections.—			*Wounds.—*	
Puerperal infections		107	Disruption	2
Endometritis	99		Wound infection	29
Acute metritis	7		Hematoma	4
Pelvic abscess	1		Wound of bladder (hysterectomy)	1
Pneumonia		14		
Acute bronchitis		11	*Thrombosis.—*	
Pyelitis		14	Phlebothrombosis	16
Cystitis		48	Pulmonary infarct	2
Acute parotitis		1		
			Gastrointestinal.—	
Hemorrhage.—			Intestinal obstruction	2
Blood loss over 400 c.c.		143	Distention (noted)	236
Delayed uterine		2	Aspiration of gastric contents	1
Retained placenta		1		
			Miscellaneous.—	
			Postpartum eclampsia	1
			Postpartum psychosis	4
			Postoperative atelectasis	3
			Cardiac decompensation	1
			Transfusion reaction	4

Hemorrhage in the course of the operation will be discussed later. Postoperative hemorrhage occurring after closure of the abdomen occurred in two cases. One patient, a 27-year-old primipara, was sectioned by the low flap technique for cephalopelvic disproportion after a labor of six hours. Blood

loss at operation was 300 c.c. Following the operation the uterus was noted to have poor tone and there was fairly steady bleeding. After four hours she was in moderate shock with blood pressure 80/52. She responded to massage, Ergotrate, and transfusions. The second patient was 42 years of age and was treated by an elective classical primary section for central placenta previa. The estimated blood loss at operation was 300 c.c. Two hours after operation bleeding was noted to be profuse and four hours later she went into profound shock. The wound was reopened and a supravaginal hysterectomy was done. Pathological examination showed no evidence of placental tissue. Bleeding had occurred from open sinuses in the lower segment. This case may offer at least one argument in favor of the low flap operation in placenta previa. While the incision might well involve some of the sinuses, it is also true that there would be some opportunity to suture them, at least along the line of the incision.

The wounds were infected in 29 cases, with an incidence of 1.9 per cent in the elective cases and 4.3 per cent in those done after trial of labor.

Thrombo-embolic disease occurred in 24 cases. More recently these cases have been treated with anticoagulants. The value of such therapy cannot be definitely assessed from this limited experience.

There were 236 cases in which distention was reported in the follow-up notes. A significant decrease in this disquieting complication has occurred in more recent years which in part may be due to early ambulation and early feeding; however, we cannot overlook the distinct possibility that in many of these cases the distention is caused by a low-grade and largely unrecognized or subclinical peritoneal infection and the improvement noted may therefore have resulted from the free use of antibactreial therapy.

There were two cases of intestinal obstruction: one responded to the use of the Miller-Abbott tube after considerable anxiety for a period of three days; the other represents the only death in this series. This patient, a primipara, was admitted in the eighth month of pregnancy because of nausea and abdominal pain. She presented considerable abdominal distention and the uterus was contracting intermittently. At first she was thought to be in early labor but the cervix was closed. The distention responded to colonic lavage. On the following day the distention recurred and she began to vomit. There was some blood in the vomitus. Based on the diagnosis of a partial intestinal obstruction a laparotomy was done. A thorough search for the obstruction revealed nothing. Since she seemed to be on the verge of labor a cesarean section seemed justified as a final step in the laparotomy. A Miller-Abbott tube was passed and there was some improvement for a while but the obstruction was not relieved. The patient died five days after the laparotomy. Postmortem examination showed the right ovary adherent to the right tube as well as to the serosa of a loop of terminal ileum by dense fibrous adhesions over an area of 3 cm. These adhesions may have been the result of a previous laparotomy which was done for appendicitis. The site of the obstruction was not recognized at operation because it was so far behind the large uterus.

Hemorrhage

In 143 cases there was blood loss of 400 c.c. or more. The amounts were estimated and for that reason this may well represent an understatement of the actual loss. Shock was reported in 27 cases. It was mild in 11, moderate in 12, and severe in 4. A total of 378 patients were transfused during or shortly after the operation. The transfusions varied from 500 c.c. to 2,000 c.c. There is an increasing trend in the use of blood as a supportive measure in patients who do not already show evidence of shock. The present policy is to make up any blood loss above 200 c.c. by transfusion quite apart from the presenting symptoms of shock. On this basis the need for transfusion in cesarean section is considerably above that required for the average laparot-

omy. Our more recent experiences have led us to insist that blood with the proper serological characteristics must be on call at the blood bank when the operation is started. This policy avoids one of the most serious errors in the management of shock, that of starting therapy too late.

Types of Operation

The low flap operation was done in 487 cases and the classical in 456. A cesarean hysterectomy was done in 54 cases, 50 of which were elective. The extraperitoneal section was done in three cases. In Table IV the types of operation according to whether or not the patients were in labor are compared. Here we note that the classical section has some preference in elective procedures while the low flap is used in increasing proportion as the possibility of infection arises.

TABLE IV. EFFECT OF LABOR ON CHOICE OF OPERATION

	ELECTIVE 663 = 100%	IN LABOR 337 = 100%	LABOR AND RUPTURED MEMBRANES 8 HOURS OR MORE 91 = 100%
Classical	55.8%	25.5%	8.8%
Low flap	36.6%	72.4%	86.8%
Cesarean hysterectomy	7.6%	1.2%	1.1%
Extraperitoneal	0.0%	0.9%	3.3%

The variations in the techniques employed in the cesarean operation aim at certain advantages for one or the other procedure. The classical operation with its fewer steps is the quickest and easiest to perform and in those few cases where speed is important because of the gravity of either the maternal or fetal condition this operation may be favored. Also, since a comparison of the immediate end results of the classical and low flap operations done in elective cases shows no significant differences, the choice here becomes equivocal and may then lie with the easier classical technique. If we had a statistically significant comparison of the late end results dealing with the integrity of the uterine scars in elective operations of various types it would throw considerable weight in support of one or the other procedure. However, the references in the literature are most unconvincing. Blood loss with the low flap operation is conceded to be less than with the classical and all other things being equal offers a good talking point for the former. In this series there was an average of 51 c.c. less blood loss in the low flap operations as compared to the classical procedures.

When we come to the choice of operation in the face of infection, potential or actual, the matter becomes the subject of a good deal of controversy. To evaluate the results obtained by the various procedures we may use first the cesarean mortality rate due to infection. In any one of the more recent series this is fortunately so low that comparisons are not statistically significant. The older series of cases are now of little value since our present practice will need re-evaluation in the light of antibiotic therapy. The rationale of the various procedures used in these cases could also be evaluated in terms of the infectious complications which do not have a fatal outcome but this presents the obvious difficulty of making the diagnosis, especially when the degree of infection is minimal. It is for this reason that the postoperative febrile reaction has been used more than any other criterion for the statistical comparison of the infections following each type of procedure. Customarily this has been expressed by the so-called morbidity rate. Quite apart from the objection that the term morbidity includes more than the infections, there is

the more serious objection that as the term is defined it does not express the degree of infection. Another specific objection as applied to the cesarean section is that a physiological postoperative febrile response may put the case in the morbid group.

With these objections in mind, for a number of years we have recorded the "Febrile Index" for all delivered cases. This may be defined as the total number of tenths of a degree of fever above 99 degrees of the peak daily temperatures for the first ten postpartum days exclusive of the day of delivery. This febrile index (FI) expresses "morbidity" in a quantitative sense. For example, in Fig. 7 it will be noted that in terms of "morbidity" the cesarean section operations in this series showed ten times more infection than the spontaneous deliveries done during the same period, while actually on the basis of the febrile index the ratio is 4:1. Likewise cesarean sections show twice the morbidity rate of the midforceps whereas actually the cesarean section operations run very little more fever than the midforceps. This conforms more with actual experience. Again in Fig. 8 where the febrile index in cesarean sections for the years 1943 to 1947 is compared to the morbidity rate, it will be noted that the febrile index shows a more consistent downward trend, which again conforms with present experience.

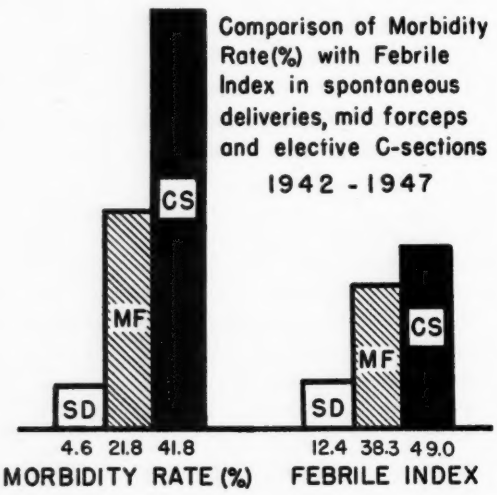

Fig. 7.

Except for the slightly greater trouble of recording the febrile reaction in this way there seems to be no reason why this quantitative measure of infection should not be the more acceptable.

TABLE V. EFFECT OF LABOR AND RUPTURED MEMBRANES ON THE FEBRILE INDEX

		INDEX
586 cases:	No labor, membranes intact	41.1
168 cases:	Labor or ruptured membranes or both up to 8 hours	59.5
129 cases:	Labor or ruptured membranes or both from 8 to 16 hours	55.3
44 cases:	Labor or ruptured membranes or both from 16 to 24 hours	74.3
69 cases:	Labor or ruptured membranes or both over 24 hours	57.4

Applying the Febrile Index to this series of cases we note first in Table V the effect of labor and ruptured membranes. The 586 elective cesarean sections showed the lowest febrile index. With varying periods of labor or ruptured membranes or both the index rises but the group having the longest

duration of labor and ruptured membranes shows a significant drop. This fall in the febrile index in the group that should theoretically show the highest index can be attributed only to the fact that these cases were most often singled out for antibacterial therapy. Nearly all of them received the drugs and most of them were treated prophylactically either preoperatively or postoperatively or both. This observation clearly indicates that this therapy has completely changed the entire aspect of the problem of infection in cesarean section.

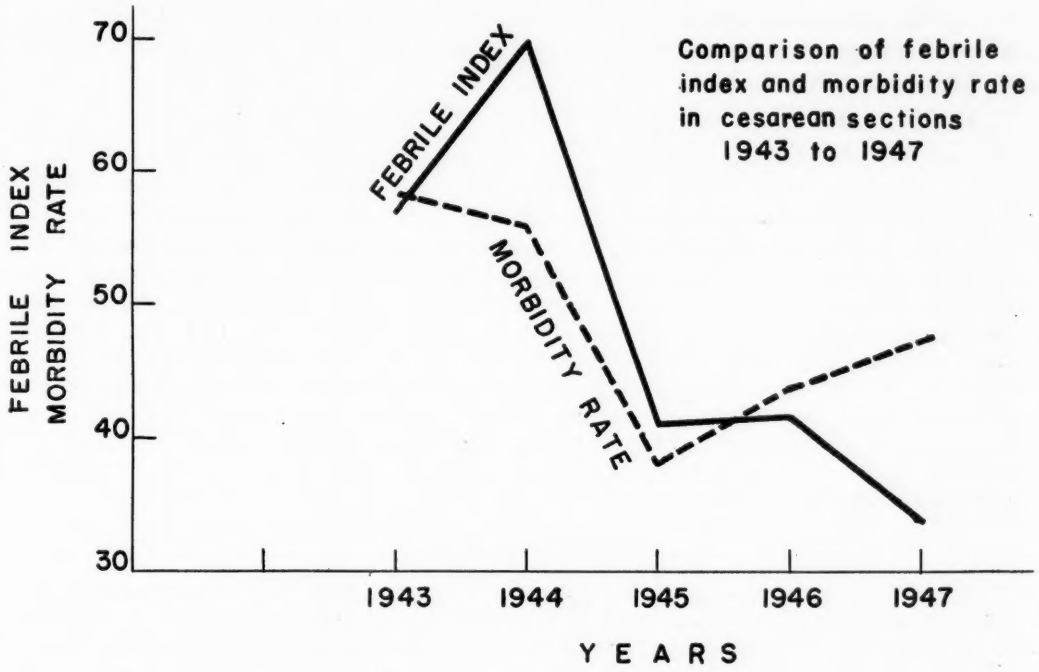

Fig. 8.

Although there is general agreement that the classical operation is not the procedure of choice when there is potential infection, there is some debate about the respective values of the extraperitoneal and low flap operations in these cases. This study does not permit us to make this comparison because our experience with the extra peritoneal cesarean is very limited. The last operation of this type was done five years ago. Our material, however, shows that we had 151 cases in which the uterus was potentially infected and 117, or 77.5 per cent of these, were treated by the low flap operation. These women were either in labor for more than twenty-four hours or they had ruptured membranes for more than twelve hours or both. Of the remaining 34 cases in this group, 27 were treated by the classical operation, 4 by cesarean hysterectomy, and 3 by the extraperitoneal route. Dividing this group into two parts chronologically (Table VI) we note an appreciable decrease in the infections with an increase in the number of cases receiving antibiotic and chemotherapy in the more recent cases. The evidence presented shows quite conclusively that under present circumstances the potentially infected patient can be delivered with relative safety by the low flap operation. It is interesting to note that in the last half of the series these potentially infected patients showed a febrile index which is very little above that for the entire group of elective cases.

TABLE VI. COMPLICATIONS IN 151 CASES OF POTENTIAL INFECTION

	FIRST HALF	SECOND HALF
Pneumonia	5	0
Infected wound	9	1
Distention and ileus	41	9
Thromboembolism	0	4
Febrile index	82.2	48.1
Antibacterial therapy	51%	76%

If the cases of potential infection can be safely managed by low flap operation supplemented with antibacterial therapy how shall we deal with actual uterine infections? With this type we have had very little experience. The three extraperitoneal sections did not fall into this group; one was a Latzko type done after thirty-three hours of labor and thirty-six hours of ruptured membranes; the second and third were Waters' operations done after eighteen hours of labor with intact membranes and nine hours of labor with twelve hours of ruptured membranes, respectively. As we see the problem of the infected uterus we believe that by careful antepartum study and recognition of abnormalities early in labor one should rarely be faced with the situation of dealing with the woman whose child is alive, whose uterus is obviously infected, and who cannot be delivered safely from below. We emphasize to our staff and student body the basic obstetric axiom that there is no truly safe way to deliver the woman with an obviously infected uterus. Should the problem arise, however, our present policy would lean toward the cesarean hysterectomy, although within the past few years we have done low flap operations in women with fever and foul amniotic fluid in a few cases without postoperative complications.

Trial Labors

In spite of this great emphasis on avoiding the situation where a cesarean section must be done in the presence of infection, trial labors were permitted in 51 per cent of all primiparas who were sectioned because of disproportion. In the younger primiparas this percentage is even higher. It seems apparent that eight hours of trial labor even with ruptured membranes present no increased hazard to the patient. With prophylactic antibiotics the trial period may be extended to twenty-four hours in cases where a reasonable doubt for the need of the operation exists.

These labors are carefully conducted. Vaginal examinations are not necessarily avoided but for the most part the study of the labor problem is carried out by abdominal, rectal, and roentgenological observations. Another more recent routine has been to give full doses of penicillin to all patients undergoing a trial of labor. The medication is continued in the postpartum period.

Cesarean Hysterectomy

The relatively large number of cesarean hysterectomies needs some comment. These are analyzed in Table VII. Practically all were elective. Of the 50 elective operations, 15 were done for fibroids and 19 were sterilization procedures. In only three cases treated by cesarean hysterectomy was the operation done to avoid potential infection. These patients were all multiparas to whom the loss of the uterus was not a serious consideration. Primiparas in the same situation have been repeatedly treated by the low flap operation.

TABLE VII. INDICATIONS FOR CESAREAN HYSTERECTOMIES, 54 CASES

18 Elective primiparas	Fibromyoma 17, accidental hemorrhage, 1
32 Elective multiparas	Fibromyoma 7, pre-eclampsia 2, placenta previa 7, cardiac 1, carcinoma rectum 1, sterilization 19
1 Nonelective primipara	Fibromyoma, section after 22 hours' trial labor
3 Nonelective multiparas	Para ii, disproportion and uterine inertia; labor 30 hours
	Para iii, disproportion not recognized; labor 28 hours
	Para iv, failure of head to engage; labor 26 hours; contraction ring

Additional Procedures

In 19 per cent of the cases some additional procedure was done, the most frequent being sterilization. This was done chiefly by the Pomeroy technique. If the 19 elective hysterectomies for sterilization are added to the tubal ligations, the incidence of sterilization is 16.7 per cent. Although the cesarean section operation is to some extent sterilizing in its effects it fortunately does not perceptibly clash with the present aspirations of most American families. Our general policy is to refuse sterilization at the first operation unless there are serious objections to another pregnancy, to accept the patient's wishes at the second operation if she expresses them, and generally to urge sterilization with the third operation. As the operation becomes increasingly safe a more conservative attitude toward sterilization is justifiable.

Anesthesia

The anesthetic of choice was nitrous oxide and ether premedicated with Demerol, 50 mg., and scopolamine 0.4 mg. This was used in 873 cases. As previously mentioned there was one fetal death due to the anesthesia which occurred when the mother received a spinal anesthetic. Spinal anesthesia was used in 73 cases. Other anesthesia used was local infiltration in 8 cases, cyclopropane in 14 cases, and a variety of miscellaneous combinations in 32 cases.

Management and Treatment

The points that we have stressed in the general plan of management and treatment are the following:

1. Proper management starts in the antepartum clinic where all primiparas and the multipara with a history of dystocia are referred to the attending staff for pelvic typing and opinion on the probable method of delivery.

2. X-ray pelvimetry is done on all cases presenting the following: Contracted pelvis; primipara with unengagement of the head; multipara with a previous history of dystocia; malpresentation.

3. Trial labors in borderline cases are given more with the purpose of ascertaining the efficiency of uterine contractions over a period of from eight to twelve hours following the onset of regular contractions rather than to determine the adequacy of the pelvis by a full test of labor which not only increases the risk of actual infection but also compromises the fetus.

4. Prophylactic penicillin in doses of 50,000 units every three hours, or 300,000 units every twelve hours is given before and after operation (a) in all trial labors; (b) in all patients whose cesarean sections were not anticipated and who have been in labor or have ruptured membranes; (c) in all cases of premature rupture of membranes, if labor does not ensue within five hours, whether cesarean section is contemplated or not.

5. Blood is on call for all cesarean sections; blood replacement is prompt and equal to the loss.

6. Early ambulation is the general rule. The patient sits up in a chair on the first postoperative day and progresses rapidly thereafter.

7. Diets progress quickly to full regular meals by the third day.

8. In patients who have not received prophylactic penicillin, the latter is given at the first sign of any abnormal temperature rise, irrespective of the presenting signs. Sulfadiazine is added soon after and given in combination if there is not a quick response.

9. The Miller-Abbott tube is used in all cases presenting evidence of ileus.

10. Anticoagulants are used routinely whenever phlebothrombosis is suspected.

Summary and Conclusions

A review of 1,000 consecutive cesarean sections performed at Sloane Hospital from 1942 to 1947 became of interest because it permitted the evaluation of this operation under present conditions of management and therapy. The increasing safety of the operation is attested by the fact that in this series, which can be further extended to 1,266 if the most recent cases are added, there was only one maternal death, making the mortality rate eight thousandths of one per cent. The reported death was unrelated to the operation. As the operation has become safer it has been substituted for the more traumatic deliveries. The data show that this trend began about ten years ago and continues at the present time. The increased incidence of the cesarean section has resulted in less trauma to mother and baby without sacrifice of maternal lives. We are aware however that steps in the right direction are often carried too far. For this reason it has been proposed and demonstrated that for a given service the cesarean section rate trend can be evaluated in the reciprocal terms of maternal and fetal trauma. Studies of this type will be required in obstetric services to avoid unwarrentedly high cesarean section rates. Even on a service in which there is a large degree of selection the traumatic deliveries and preventable fetal deaths can each be reduced to a figure that is under one per cent with a cesarean section rate of near 6 per cent. For unselected services the incidence could be lower.

The indications for the operations show that placenta previa has reached third place and presents the most striking upward trend. There is apparent a variable degree of broadening of the scope of the operation in all categories except for rheumatic heart disease where the trend is downward.

The complications enumerated give evidence of the fact that although the antibiotics were used extensively there is still the problem of infection. Acute endometritis was frequently observed. Prophylactic penicillin has been used in the past two years and as a result the infections, even the minor ones, have decreased. We strongly advocate the use of prophylactic antibiotics in all patients who may require operative intervention. Hemorrhage will always be a problem in cesarean section because of the very nature of the procedure but its tragic effects have been minimized by having blood on call for all cases.

A new measurement of the febrile reaction following operation has been proposed which is termed the "febrile index." It expresses fever quantitatively. Using this index it was shown that the amount of postoperative

fever rises with the duration of labor and ruptured membranes preceding the operation except for the group that had the longest period of labor and/or ruptured membranes. This may seem paradoxical but since it was this latter group that was treated with antibacterial drugs most intensively, this is offered as the only apparent explanation for these unusual findings.

The data also show that the low flap operation in conjunction with antibiotics given before and after operation is a safe procedure when there is potential infection. On the basis of this experience we see no reason to use the extraperitoneal cesarean section in this group of cases. We have had only limited experience with the neglected case that presents actual infection.

Management and therapy have been indicated and stress the importance of careful appraisal of the obstetric prognosis, of prophylactic antibiotic therapy, and the need for adequate amounts of readily available blood on hand for all cases.

De Voe, Robert W., and Hunt, Arthur B.: Manual Removal of the Placenta: A Ten-Year Survey, Proc. Staff Meet. Mayo Clin. **23**: 414, 1948.

From 1936 through 1945, about 6,750 obstetric patients were treated at the Mayo Clinic and, in this period, manual removal of the placenta was done in ninety-eight cases (1.4 per cent). For this procedure the field is reprepared with aseptic technique. One hand of the obstetrician is placed in the uterine cavity to bring the fundus forward where it is held with the other hand placed on the anterior abdominal wall. A cleavage plane between the placenta and the uterine wall is sought, and dissection is carefully done by hand. The placenta is removed as a whole. In sixty-eight of the cases the uterus was packed with iodoform gauze. In eighteen of the cases in which removal of the placenta was done, complications had occurred in a previous pregnancy, including spontaneous abortion in eleven cases. In the pregnancy considered in this report some complications had occurred in twenty-eight cases, including placenta previa in eight cases. Operative delivery was employed in thirty-three of the ninety-eight cases in this series, or 34 per cent, including outlet forceps in nineteen cases.

In eighty-nine cases manual removal of the placenta was done in patients delivered at the clinic and under favorable circumstances. In twenty-one of these cases the placenta was removed because of prolonged retention (average time 69.3 minutes); in three cases because of bleeding; and in thirty-two cases because of both prolonged retention and bleeding (average time of retention 51.7 minutes). In six cases retention of the placenta was due to a pathologic contraction ring and in three cases the placenta was incarcerated by the cervix. There were six cases of marginal placenta previa and two of central placenta previa, and two cases of fibromyoma of the uterus; in one case the placenta was removed because of severe anemia. In nine of the ninety-eight cases, the patients had been delivered or had received preliminary obstetric treatment elsewhere before being brought to the clinic; in these cases conditions were not so favorable; the placenta had been retained for a long time, a hemorrhage had occurred, or there had been opportunity for contamination. The only death in the series occurred in this group and was due to puerpreal sepsis; this was a case of multiple pregnancy (triplets) with incarceration of the placenta by the cervix.

In the group of eighty-nine cases in which manual removal of the placenta was done early under favorable circumstances, the puerperal morbidity rate was 4.5 per cent; in the nine cases in which treatment was delayed, the puerperal morbidity rate was 77.8 per cent.

HARVEY MATTHEWS.

RECENT TRENDS IN CESAREAN SECTION*

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AN INCREASED interest has developed during recent years in the use of cesarean section due to the introduction of new agents to combat infection, improved supportive measures, and the standardization of surgical techniques. Recently, we[1] reported a decreased morbidity and a liberalization of the indications for the low flap type of operation. The study was based on a limited experience in which all of the above principles were applied. Since that time we have accumulated more data to substantiate our previous conclusions and to clarify further the indications for the transperitoneal low flap operation in complicated labors.

As a result of recent advances in pre- and postoperative therapy, surgeons[2] are at present able to perform extensive intestinal procedures with primary anastomoses where contamination is inevitable. The bowel may now be treated preoperatively with appropriate sulfonamides so that the entire intestinal flora becomes markedly reduced. With adequate dosage of the antibiotics and sulfonamides postoperatively, the peritoneum is capable of eliminating a large amount of bacterial contamination. In addition to chemotherapy, intestinal suction, careful control of fluid and electrolyte balance, rapid blood replacement, parenteral amino acids and vitamin therapy have improved healing, diminished infection, and reduced the risk following intraperitoneal surgery. The change is further reflected in the treatment of peritonitis following appendicitis in which drains are rarely placed in the pertioneal cavity. The peritoneum, with the advantages of modern postoperative therapy, is able to control the infection adequately. It is with these same pre- and postoperative aids that we have performed cesarean sections, particularly during the past three years.

Early experience with the sulfonamides[3] indicated clearly that they were of great value if employed prophylactically but might prove disappointing when used after an obvious infection was established. We, accordingly, have employed sulfadiazine since 1942 when infection was anticipated. After penicillin became available, we instituted it also as a prophylactic agent. Our present indications for this combined therapy are as follows: (1) ruptured membranes and twelve hours of labor with delivery not imminent; (2) intact membranes and twenty-four hours of labor with delivery not imminent; (3) questionable dystocia or abnormal presentation with trial of labor; (4) desultory labor, ruptured membranes, and anticipated prolonged labor; (5)

*Read at a meeting of the New York Obstetrical Society, Oct. 12, 1948.

anticipated cesarean section or difficult delivery; (6) intrapartum infection or intercurrent infection; (7) uterine hemorrhage, intrapartum or postpartum.

The penicillin and sulfadiazine have been used, as reported previously, without serious toxic effects. The usual dosage is 6 Gm. of sulfadiazine and 160,000 units, or more, of penicillin G in divided doses daily. Recently, we have employed penicillin G in saline or in procaine in a dosage of 300,000 units once or twice daily. Streptomycin has been added occasionally as a third antibacterial agent.

Following the advent of the modern surgical era in the latter part of the last century, various techniques were introduced to diminish the possibility of peritonitis subsequent to cesarean section. A number of these methods, such as vaginal section, peritoneal exclusion, and exteriorization of the uterus have been discarded in this country. The low flap operation, first described in 1805, was popularized in this country by Beck, DeLee, and others. The principle employed in this procedure involved an initial contamination of the peritoneal cavity but the prevention of subsequent insults. The extraperitoneal approach was employed with some regularity in Germany beginning about 1908. The operation was done infrequently in the New York Lying-In Hospital as early as 1915. It was Jellinghaus, however, in this institution, who in 1923 initiated a real interest in the procedure in this country for the delivery of patients with intrapartum infection.

Steele,[4] in 1930, reported fifty-nine Latzko sections with complications such as perforation of the peritoneum ten times, three instances of vesicovaginal fistula, a vesicouterine fistula, and nineteen wound infections. Subsequent reports by Fellows of this Society, Burns,[5] Sackett,[6] Norton,[7] Cosgrove,[8] Aldridge,[9] Waters,[10] Marr,[11] and Williamson and Goldblatt[12] constitute a large part of the American literature on this subject.

Irwin[13] wrote in 1941 that although extraperitoneal sections were used in Europe for thirty years and in America for seventeen years, very few clinics were familiar with the procedure and less than twenty reports of its use were in the American literature for the preceding ten years. He further stated that "the failure and neglect to use this technique have been due to fear of complications rather than lack of confidence in it." In 1940 Waters[10] and Ricci[14] independently reported the use of supravesical techniques which they thought simplified the operation and reduced complications. Waters[15] stated in 1945 that he had 68, or 27 per cent, peritoneal injuries and four bladder perforations in 250 cases. Daichman and Pomerance[16] used the Waters technique in 100 cases and reported 42 peritoneal injuries and 15 bladder perforations. They found that most cases had drainage from the wound over a period of two weeks. Recently, in 1946, Norton[17] reported a paravesical approach in 160 cases with 9, or 5 per cent, injuries to the bladder and 27.5 per cent to the peritoneum. No permanent fistulas were found by these authors.

In a report of all cesarean sections for the state of Massachusetts from 1937 to 1941, DeNormandie[18] found that only 1.2 per cent of 11,030 reported sections were of the extraperitoneal type. This would indicate that during this five-year period only a small portion of potential and infected cases were being sectioned in the state of Massachusetts by extraperitoneal operation. Although scattered reports of the extraperitoneal section continue to be published, it appears that only a few clinics regularly employ this procedure.

Dieckmann and associates[19] have recently reviewed the indications for cesarean hysterectomy at the Chicago Lying-in Hospital. Out of a total of 153 cesarean hysterectomies, 21 were performed in infected cases and 12 in the potentially infected group. The only death in the series occurred in 1937 from peritonitis after twenty-one hours of labor with ruptured membranes for forty-five hours. These authors believe that the extraperitoneal section is indicated in the potentially infected case and cesarean hysterectomy in the truly infected patient.

In the three years under study at the New York Lying-In Hospital, 1946 through 1948, no hysterectomy was performed for prolonged labor and infection. The indications for hysterectomy were chiefly fibroids in elderly multiparas, occasionally for uterine hemorrhage, and rarely for rupture of the uterus. For sterilization, tubal ligation was used in our series. In the infected group of cases, the method of choice was transperitoneal low flap section and no uteri were sacrificed.

Since the opening of the Lying-In Hospital at its present location in September, 1932, to July, 1948, 54,937 deliveries and 1,622 cesarean sections were performed. The incidence of cesarean sections for this period was 2.9 per cent with a maternal mortality of 1 per cent (Table I). McCormick[20] has compiled data from twenty of the country's leading clinics for the five-year period 1941 to 1945, inclusive. In a total of 245,000 deliveries, the section incidence was 3.3 per cent with a mortality rate of 0.61 per cent. The highest incidence reported in this group was 7.06 per cent from the University of Pennsylvania and the lowest from Emory University was 0.51 per cent. Mortality varied from zero to a little over 2 per cent. During the same five-year period on our service, the section incidence was 3.3 per cent with a maternal mortality rate of 0.38 per cent.

TABLE I. 1932-1948

Total deliveries	54,937
Total cesarean sections	1,622
Incidence	2.9%
Maternal mortality	1.0%

The annual number of sections performed was about the same from 1933 through 1941 with a progressive increase since that time. The incidence from 1933 to 1941 varied between 2 and 3 per cent (Fig. 1). For the last four years, however, our incidence has been 4 per cent. This increase in the incidence of cesarean sections is due largely to a change in our concept of indications. In a review of this subject in our hospital, it is apparent that we are doing more sections at present for desultory prolonged labors, fetal asphyxia, elderly primiparas, and prolapse of the cord. In contrast to the earlier years, elective operation for dystocia without adequate trial labor is now seldom performed. The decreased risk associated with the procedure undoubtedly has increased its applicability.

The data on maternal mortality (Table II) are divided into approximately three equal periods. From 1932 to 1937 there were nine deaths; from 1938 to 1942, four; and from 1943 to 1948, three. In the first period, 1932 to 1937, five of the nine deaths were due to peritonitis, three to hemorrhage, and one to heart disease. In the second period, pulmonary embolus was the main cause of death although there was one death from hemorrhage and a second from infection. In the third period, 1943 to 1948, no deaths resulted from peritonitis or hemorrhage. Two deaths were caused by malignant tumors, one an adenocarcinoma of the liver and the other a neurogenic sarcoma in the pelvis. The third death in the recent group was caused by a fulminating bilateral

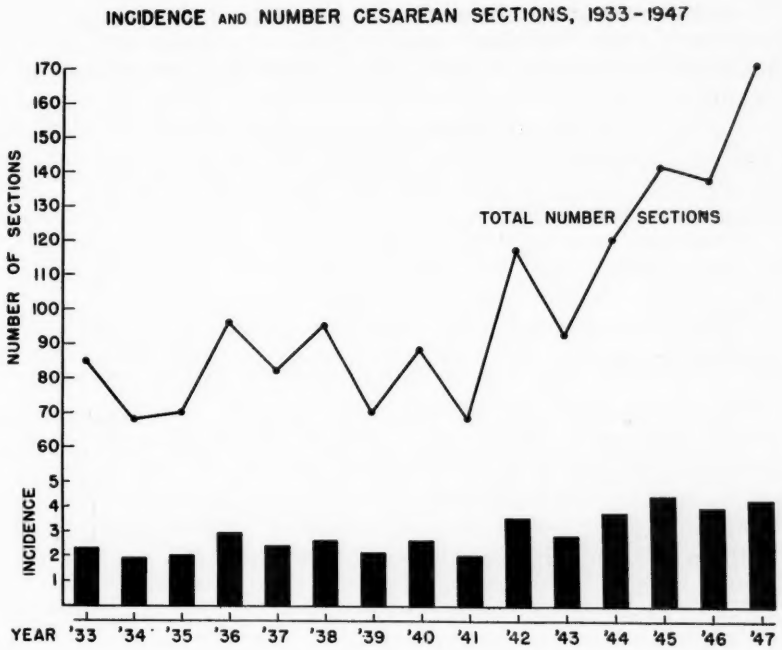
INCIDENCE AND NUMBER CESAREAN SECTIONS, 1933-1947
NUMBER OF SECTIONS
170
160
150
140
130
120
110
100
90
80
70
60
TOTAL NUMBER SECTIONS
INCIDENCE
5
4
3
2
1
YEAR '33 '34 '35 '36 '37 '38 '39 '40 '41 '42 '43 '44 '45 '46 '47

Fig. 1.

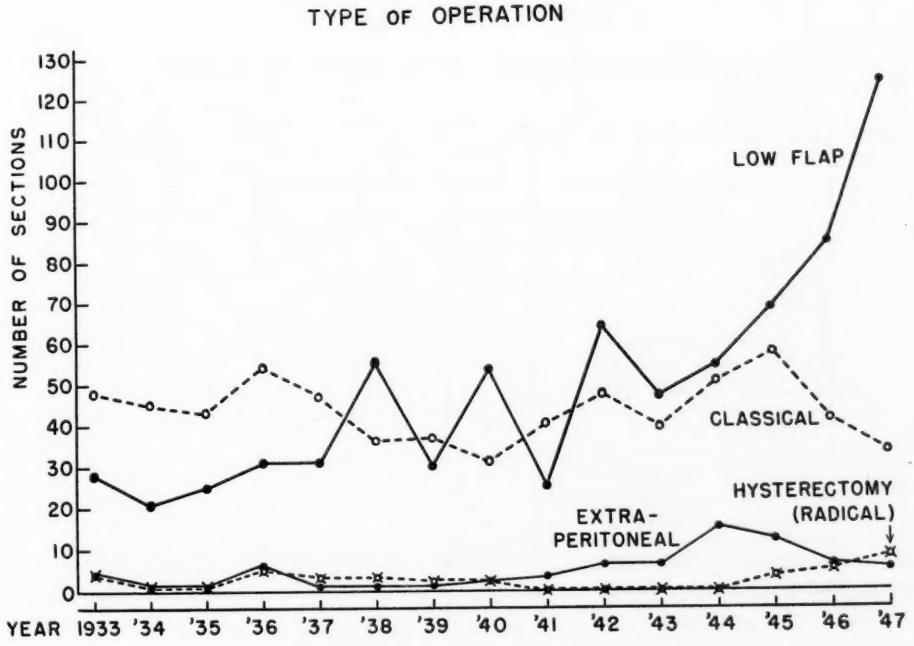
TYPE OF OPERATION
NUMBER OF SECTIONS
130
120
110
100
90
80
70
60
50
40
30
20
10
0
LOW FLAP
CLASSICAL
HYSTERECTOMY
(RADICAL)
EXTRA-
PERITONEAL
YEAR 1933 '34 '35 '36 '37 '38 '39 '40 '41 '42 '43 '44 '45 '46 '47

Fig. 2.

renal cortical necrosis. In each of these instances, the disease responsible for the death constituted the indication for the operation. It is of interest to note the absence of a maternal death from peritonitis from 1940 to 1948 despite the great increase in sections performed after twelve and twenty-four hours of labor.

TABLE II. CESAREAN SECTION MORTALITY

	1932-1937	1938-1942	1943-1948
Causes.—	9	4	3
Peritonitis	5	1	0
Hemorrhage	3	1	0
Embolus	0	2	0
Neoplasm	0	0	2
Cardiac	1	0	0
Renal necrosis	0	0	1

Fig. 2 illustrates the general trend in the type of operation during the years 1933 through 1947. From 1933 to 1937, the classical type and the low flap were used with about equal frequency. Since 1947, the low flap has greatly superseded all other techniques. In 1947, about three-fourths of the sections were performed by the low flap method. The extraperitoneal operation was seldom performed before 1940. Thereafter, the number increased to a peak in 1944. Since that year the number has gradually fallen despite the larger number of sections performed after twenty-four hours of labor. In 1947 there were only five extraperitoneal sections and these were done chiefly for teaching purposes. The cesarean hysterectomy continues to be performed on rare occasions. These data clearly indicate the great increase in the use of the low flap transperitoneal section and a reduction in the classical and extraperitoneal varieties.

TABLE III

ANALYSIS OF SECTIONS, OVER 24 HRS. OF LABOR

	1946	1947	1948*		TOTAL
TOTAL SECTIONS	136	169	114		419
24 HRS. LABOR +	16	30	24		70
LOW FLAP	14	28	19		61
EXTRAPERITONEAL	2	2	5		9
POSTOP. HOSP. DAYS	13.5	12	11.4	AVERAGE	12
MORBIDITY	7	8	8		23
UTERINE INFECTION	5	5	7		17
WOUND INFECTION	2	1	1		4
URINARY INFECTION	0	2	0		2

* INCLUDES SECTIONS JAN. TO JULY 1948

From January, 1946, to July, 1948, seventy patients, or one-sixth of the total number on whom sections were performed, were in labor over twenty-four hours (Table III). The majority of indications for operation were pro-

tracted desultory labor with lack of progress, fetal distress, or, more rarely, cephalopelvic disproportion. Nine of the seventy sections were extraperitoneal, either by the Latzko or Waters technique. All the others were of the low flap type. The postoperative stay in the hospital averaged twelve days which was slightly longer than in the elective cases. Sixty-five patients received prophylactic penicillin and sulfadiazine during labor; one received the drugs therapeutically following operation. Three received penicillin alone prophylactically and a single patient received no chemotherapy at all; the latter was a private patient, in labor for twenty-eight hours with intact membranes. The total morbidity for this prolonged labor group was 32 per cent, which is the same for all sections in 1946 and 1947. Only one patient developed an intrapartum infection with a temperature of 38.4° C. for a single day. In this particular case, the postoperative course was afebrile. There was no evidence of infection among the newborn and one infant died in the neonatal period of congenital anomalies. The total number of morbid patients was twenty-three (32 per cent) and in these cases the membranes were ruptured an average of twenty-four hours. It was thought that in seventeen cases there was intrauterine infection. The febrile reactions were mild and of short duration and in only two instances lasted as long as five days. Four wound infections developed of which two were mild in character. The other two had protracted temperature elevations for eight and ten days. The longest febrile case in the group was a wound infection following an extraperitoneal section which required secondary closure. There were two instances of urinary infections; both were mild and one complicated diabetes mellitus. Nineteen of the morbid group had low flap sections and four, the extraperitoneal type operation.

TABLE IV

TREND IN CESAREAN SECTION

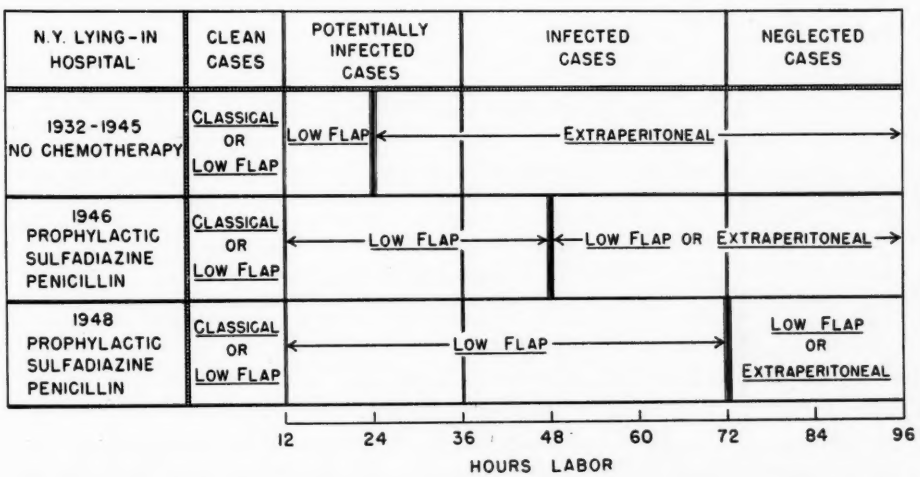

Table IV illustrates the type of section performed during three periods, in patients in labor with ruptured membranes. Prior to the advent of modern preoperative surgical preparation, including prophylactic penicillin and sulfadiazine, the low flap section was performed usually before twelve hours of labor. In 1946, at the onset of the routine use of prophylactic chemotherapy, the indications for the low flap type of operation were extended to include patients with ruptured membranes in labor for two days. Finally,

in 1948, the low flap section was further extended to all patients, irrespective of the duration of labor. The extraperitoneal section has been occasionally employed in patients with protracted labors for teaching purposes. Since 1945 we have not been impressed with the necessity for an extraperitoneal section. The classical procedure was usually performed in clean cases after a labor of less than twelve hours with intact membranes, or in patients in whom the lower uterine segment was poorly developed, or when a rapid delivery was required for placenta previa, premature separation of the placenta, or fetal asphyxia.

Our experience with neglected cases is rather limited but we have encountered instances where delivery through normal birth passages had to be abandoned because of the probability of serious injury to mother or baby. We have unhesitatingly done the low flap operation after attempted forceps, repeated vaginal examinations, and other intrauterine manipulations. On several occasions the umbilical cord was maintained manually in an intrauterine position until the baby was delivered. We have had the opportunity to see patients with protracted labor in other institutions. These cases include attempted forceps delivery and those with many vaginal examinations where no chemotherapy was instituted up to the time of operation. Both drugs, however, were maintained during the early puerperium and the puerperal course was entirely uneventful.

Discussion

Mortality following cesarean section has been due chiefly to hemorrhage, infection, and complications as a result of anesthesia. Our data indicate clearly that infection may be eliminated as a cause of mortality or as a serious complication when the low flap operation is employed, even in the presence of infection. By adequate exposure, this approach affords the operator a much better opportunity of controlling hemorrhage. Unanticipated abnormalities, such as ovarian or uterine tumors, extreme atony of the uterus, or other intra-abdominal disease, may be recognized and appropriate measures adopted. A recent example occurred in a patient with prolonged labor. The unexpected finding at the time of operation was a pedunculated ovarian cyst with a small perforation. Obviously, this potentially serious complication would not have been recognized if we had elected to employ the extraperitoneal approach in this patient.

Our experience and that of others has demonstrated that blood loss is at a minimum when local-block procaine anesthesia is employed. No other anesthetic is as safe or has as few complications. In the extraperitoneal operation, however, it cannot be utilized with any regularity because of exposure difficulties and the need for greater relaxation. The transperitoneal low flap operation may be done under local anesthesia when indicated. There is little or no danger of injury to adjacent structures, such as bladder, ureter, and the main branches of the uterine arteries. In addition, our experience indicates that the postoperative course is less complicated and the primary wound healing is encountered more frequently. In fact, the only instances in recent years with significant wound infection occurred when the extraperitoneal approach was employed.

Our hospital is a large teaching institution, intimately associated with the medical school. A full-scale program for undergraduate and graduate in-

struction and training is in progress. Our primary consideration, at all times, is the welfare of the patient. The resident staff is trained in both obstetrics and gynecology and performs practically all of the surgery on our pavilion (ward) service. They are capable of acquiring the necessary technical skill to perform the extraperitoneal operation. With the limited number of opportunities none could be considered proficient. It appears then that if the resident staff is to be trained in this operation, radical changes in indications would become necessary. We believe that from the present data the change is not justifiable. A searching investigation of our experience with prolonged labor and other complications during the last three years has failed to reveal any case in which the low flap operation could not be undertaken with safety.

Conclusions

1. At the Woman's Clinic, New York Hospital, the incidence of cesarean section has increased from 2 to 4 per cent during the years from 1933 to 1947.

2. The low flap transperitoneal section has gradually replaced the classical and extraperitoneal techniques.

3. A review of maternal mortality at this clinic indicates an absence of deaths from infection during the past eight years.

4. Seventy cesarean sections preceded by over twenty-four hours of labor are reported in a series of 419 consecutive sections since the use of prophylactic combined chemotherapy from January, 1946, to July, 1948.

5. Sixty-one were performed by the low flap technique and nine by the extraperitoneal route. No serious infections were encountered.

6. With the prophylactic use of modern surgical supportive therapy, including chemotherapy, electrolyte and fluid balance, adequate nutrition, and intestinal intubation, the extraperitoneal or radical cesarean sections have not been indicated.

7. The low flap section is simpler to perform, is without adjacent structure injury and is without protracted wound drainage.

8. Peritoneal surfaces may adequately care for large amounts of bacterial contamination if the source of such infection is limited and chemotherapy is instituted early.

9. When gross negligence results in intrapartum infection which cannot be controlled, extraperitoneal section or cesarean hysterectomy may be indicated. We have not observed any patients in this category in recent years.

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Discussion of Papers on Cesarean Section by Dr. D. Anthony D'Esopo and by Drs. R. Gordon Douglas and Robert Landesman

DR. WILLIAM E. STUDDIFORD.—The results that have been obtained in the performance of cesarean section on the Obstetrical Service at Bellevue Hospital confirm those presented here. Beginning in June, 1940, a policy was instituted whereby all patients who were subjected to cesarean section after they had been in labor with ruptured membranes were treated with sulfonamides. In addition, in the last few years they have also been given penicillin. Up to Oct. 1, 1948, there were 14,671 patients delivered, 387 of them by section. That is an incidence of 2.65 per cent which is strikingly lower than the figure cited by Dr. D'Esopo. I do not believe that our incidence has changed a great deal. However, it may have risen slightly in the past few years. Of these cases, 160 were elective operations, and many of the patients were delivered by the classical operation. There was one death in the group, a patient with placenta previa and pre-eclampsia and fibroids. She hemorrhaged severely at the time of operation and died four days postoperatively of an ileus. Autopsy showed no evidence of any infection. There were 227 patients in the series delivered after a trial of labor and these were uniformly done by the low flap type of operation. There were no deaths in this group.

We have not done any extraperitoneal operations since June 2, 1940.

This gives a mortality, on a service which has taken care of a great many emergency cases that we have not been able to study in the antepartum period, of 0.26 per cent.

DR. SAMUEL A. COSGROVE.—I feel that I am impelled to speak because our viewpoints, and I say viewpoints because I am sure the three chiefs of our own services share them and are united in holding them, are so radically different from the viewpoint expressed. We make extensive use of cesarean section. The rate, as in Dr. D'Esopo's experience, is increasing. I do not know where Dr. D'Esopo got the very low rate for our service that he showed; it was probably from some early communication. In the last ten years our rate has been 3.3 per cent, and last year it was 4.4 per cent. There is a definite increase in our incidence of cesarean section on very much the same basis which was discussed.

I am particularly happy to subscribe to Dr. D'Esopo's belief that the increasing incidence of cesarean section, paralleling the elimination of difficult vaginal delivery, is wholly salutary and will, I hope, increase until, as he has said, anything but the simple operative vaginal deliveries will be completely obsolete in our experience.

But the use of extraperitoneal section in our hands is very much greater than in either of the other clinics. The reason for this naturally is due to the success which has attended our use of this technique. I will admit perfectly freely that we are perhaps riding the hobby hard in our clinic, because we have represented there the proponents of what I think are the two best extant techniques of that operation.

Our educational program is wholly postgraduate and inasmuch as we believe very thoroughly that every competent obstetrician should have in his armamentarium facility in the use of the extraperitoneal section, we use it largely as a teaching facility.

Entirely apart from that, while I by no means derogate the contribution that the sulfonamides and the antibiotics have made to our modern resources of safety for patients, I

do not feel that they should displace good surgical judgment in any field and that they should not be relied upon to displace safer operative procedures, which we believe the extraperitoneal operation to be.

Several years ago, when we were just beginning to be interested in the more extensive indications for the extraperitoneal section that we recognize today, Dr. Waters published a study in which he showed that in periods of duration of labor and periods of ruptured membranes, the mortality and morbidity rates, particularly the latter, ascended sharply after certain limits of those phenomena were passed. Dieckmann, Douglas, and others have shown a similar correlation between postoperative mortality and morbidity and the use of the transperitoneal section in relation to the duration of labor and the duration of ruptured membranes. In a recent survey of our own we found that that difference in morbidity has been entirely eliminated. In other words, there is no essential difference in our postoperative morbidity as between those patients who have been in labor a short time and over long periods, and as between those who have had ruptured membranes a short time and those who have had ruptured membranes a very long time.

We cannot gainsay the value of the sulfonamides and of penicillin in that elimination of the difference in morbidity, but we do not believe that they account for it all. We believe that the application of strict criteria limiting the transperitoneal approach in favor of the much safer and not tremendously more difficult extraperitoneal approach, is responsible for this change rather than the availability of the sulfonamides and antibiotics.

DR. RALPH L. BARRETT.—I am glad to note that there is a definite tendency toward higher incidence of cesarean section in the last ten years. Some fifteen or twenty years ago at the Woman's Hospital, we began to increase our incidence of section, largely in the treatment of placenta previa and premature separation and in the borderline pelvis with poor progress in labor frequently noted as cephalopelvic disproportion. We also selected cesarean section rather than delivery by bimanual dilatation of the cervix and delivery by mid- or axis traction forceps in the more protracted labors.

With this increase in incidence of cesarean, our maternal mortality and morbidity showed a definite drop and there was decided decrease in our fetal and neonatal mortality.

Classical cesarean is rarely used in the Woman's Hospital. Our choice is the low flap type. We do use extraperitoneal cesareans for the frankly infected or potentially infected cases. We are firm believers in the merits of the extraperitoneal operation in these cases.

DR. EDWARD G. WATERS.—We have been doing the low transverse cervical operation since our hospital (Hague Maternity) was opened. Since 1929 I have done but two classical sections. The usual operation is the low flap popularized in this country by DeLee, Phaneuf, Beck and the Brooklyn group, and others. It is very encouraging after twenty years to find that these two outstanding clinics have finally accepted the low transverse operation as a good procedure. In the years ahead, as the technique of the not-too-difficult extraperitoneal operation becomes more familiar and as more learn how rather than find excuses for not doing it, the operation will have greater use than it has today. I use it in private practice frequently in clean and elective cases because of the good postoperative recovery with early ambulation which permits return home by the tenth day.

The experience with our own private patients, covering a period of nearly four years, shows a high incidence of section, for there were 109 operations, or 6.5 per cent, in 1,617 deliveries. Thirty-one per cent represented elderly primiparas over 35 years of age, and about the same number and per cent were for repeat sections. Of the 109 operations, 59 were of the low transverse type and 50 were supravesical extraperitoneal sections. Seven of the latter patients had previously had low transverse operations. Almost all of the extraperitoneal cesareans were elected to demonstrate technique. Only one was necessitated by infection. Gross infection today should be a rarity, and the extraperitoneal cesarean section is therefore more often elected in potential infection and because of the smoother postoperative course.

We use all of the methods for the patient's protection that have been mentioned tonight, although our penicillin dosages are greater. In 46,000 deliveries there were 1,490 sections, representing an incidence of 3.2 per cent. There were 501 extraperitoneal sections with one death, or 0.2 per cent. In the last 450 of the extraperitoneal cases there were no deaths. We had a considerable number of disturbing complications; placenta previa with accreta, for instance. In 127 sections for placenta previa there were two deaths; one from placenta accreta. There were 99 sectioned abruptions with one death. This totals but three deaths in a series of 701 placenta previas and abruptions. There are no corrections made for any deaths. In the extraperitoneal group the death rate is 0.2 per cent. The uncorrected gross section mortality is 0.67 per cent.

Our management of cesarean section cases includes properly timed use of transfusions, chemotherapy, antibiotics, sedation, anesthesia, and general supportive measures. It also includes extraperitoneal cesarean section. I cannot see why in this day anyone will accept one and reject another procedure when the use of both will further help to reduce mortality. If we accept as advances in therapy, sulfonamides, penicillin, streptomycin, and the like, we should certainly accept a procedure which will keep the operative field out of the peritoneal cavity. Who here will dare to say that no patient now need die from peritonitis because of our new antibacterial aids? I have seen patients die from peritonitis who have had plenty of sulfonamides, penicillin, streptomycin, and blood. Therefore, if peritoneal contamination in septic cases with resulting possibly fatal peritonitis can be avoided and may be achieved by mastering a not-too-difficult technique, then I believe we are morally bound to give our patients this added protection. Given a potential candidate for peritonitis, with or without sulfonamides and penicillin, I would be derelict in my duty if I did not keep out of the peritoneal cavity. The extraperitoneal approach is not frequently necessary, but is wisely selected in all questionable cases. It completely supplants cesarean hysterectomy in septic cases. The potentially infected patient needing cesarean is entitled to its protection.

DR. D'ESOPO (Closing).—It is only natural that the discussion should revolve around the relative merits of the extraperitoneal section as opposed to other types of the operation in the cases of potential infection. This subject has always been controversial. The best argument that we have for the low flap operation in so far as its adequacy in cases of potential infection is concerned, is that we have been able to get along without the use of the extraperitoneal operation and the results obtained have been entirely satisfactory. A mortality rate of one-tenth of one per cent is exceedingly low.

The most striking group of patients in this series were those with potential infection. During the last three years in particular, with intensive use of antibacterial therapy, their postoperative course was smooth and uncomplicated, as I have already shown. The degree of febrile reaction in this group of cases was not very much above that noted for the entire elective group.

It is my feeling that none of the arguments presented by Drs. Waters and Norton contradict the validity of the conclusion expressed here tonight, that the low flap operation provides a satisfactory way of managing the potentially infected woman.

There is an important point that we should not forget, namely, that the relative value of these operations in the infected patient must be reassessed in the light of antibiotic and chemotherapy. The old statistics are not too important for it well may be that the peritoneal cavity with its greater ability to concentrate penicillin and sulfonamides may present more resistance to infection than the infraperitoneal cellular tissue which is exposed to infection in the extraperitoneal operation. The critical experiment, then, in evaluating these two operations in the face of actual infection still remains to be done.

DR. DOUGLAS (Closing).—I was particularly interested in the remarks of Drs. Cosgrove, Norton, and Waters of the Margaret Hague Maternity Hospital because of their large experience with the extraperitoneal approach in this procedure. The similarity in incidence between the figures quoted by Dr. Cosgrove for the Margaret Hague, Dr. McCormick's collected statistics, and the figure we quoted, i.e., 3.3 per cent, is striking. I cannot

agree completely with Dr. Waters' statement regarding the relative value of antibiotics and sulfonamides. Moreover, I made the point that potentially infected patients adequately protected with these agents can be subjected to transperitoneal double flap procedures with the same or greater margin of safety than may be obtained by the extraperitoneal operation. Our patients are out of bed on the first postoperative day and frequently discharged prior to the tenth postoperative day.

During the past three years almost 500 patients a month have been delivered at the New York Lying-In and Mt. Vernon Hospitals and I have been looking for but have not found a real indication for the extraperitoneal section. Our data presented clearly indicate that there is no superiority of the extraperitoneal over the transperitoneal approach. In fact, primary wound healing is better and other complications are encountered less frequently with the latter procedure.

I do not know whether Dr. Heaton referred to a comment that I made when he objected to the relegation of the extraperitoneal section to history. I did not make that comment, but stated that vaginal cesarean section, exteriorization of the uterus, and peritoneal exclusion operations had been discarded in this country. I did not include the extraperitoneal section.

Like Dr. Waters, Dr. Cosgrove, and Dr. Norton, I am anxious to see the best results obtained. Certainly, if they can be achieved by one group by means of the extraperitoneal section, then it becomes the method of choice for their clinic. If better results by another group can be obtained by the low flap procedure, then it is the method which the second group should employ.

Feeney, J. K.: Cesarean Section in Dublin, Irish J. M. Sc., Sixth Series, No. 276, page 755, Dec., 1948.

The author has studied cesarean section incidence in three large maternity hospitals in Dublin for the years 1932 to 1946, inclusive, using only hospital deliveries. During this time there were 108,140 deliveries with 2,273 cesarean sections. This gave a rate of 2.1 per cent. The maternal mortality rate was 2.7 per cent with a fetal mortality rate of 11.4 per cent. There were 1,415 primary sections. These were considered under the headings of maternal and fetal mortality, operative and postoperative complications. There were 858 repeat cesarean sections. The fetal mortality in this repeat group was 6.7 per cent. The incidence of rupture of a previous cesarean section scar was 1.9 per cent. During the period under observation, 148 cases with previous cesarean section were allowed to deliver from below. The criteria for decision to allow a patient with a previous section to deliver from below are given in detail. L. M. HELLMAN.

Brown, J. A.: Cyclopropane in Cesarean Section, Canad. M. A. J. 59: 464, 1948.

The author reviews a series of 378 cases of cesarean section using general anesthesia with cyclopropane with one maternal death (not directly ascribed to the operation or to the anesthetic) and a net loss of three infants. Cyclopropane combines low toxicity, rapidity of action, and a high oxygen content. Prematures do exceedingly well with cyclopropane. The superiority of cyclopropane lies in the contentment of the patient under general anesthesia as compared with regional anesthesia. In cases of shock, cyclopropane is the ideal anesthetic. In general, the ideal anesthetic in cesarean section should provide anesthesia safely and satisfactorily to the mother, while subjecting the fetus to few or none of the toxic effects of the agent. WILLIAM BERMAN.

A FIFTEEN-YEAR SURVEY OF CESAREAN SECTIONS

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THE problem of cesarean section is one of increasing interest and prominence concerning its role in obstetrical surgery. A survey of the cesarean sections done at the Milwaukee Hospital during the past fifteen years was made, dividing this period of time into five-year intervals with more detailed analysis of the last five years. The study includes 1,231 cesarean sections performed on private patients from Jan. 1, 1933, to Dec. 31, 1947. The series is consecutive and includes all cases found in the cross-file index in the record department.

Incidence

There were 1,231 operations performed among 19,890 deliveries, an incidence of 6 per cent. In Table I the incidence is divided into three five-year periods and shows a decrease from 7.5 per cent in the early period to 5.4 per cent in the last period. During the period from 1943 to 1947, consultation with another staff member was required prior to operation. Almost one-half (43.4 per cent) of these operations were repeat cesarean sections, making the primary section incidence 3.05 per cent. While the incidence in this hospital shows a progressive decrease, statistics from the Wisconsin Bureau of Maternal Health show a steady rise throughout the State. The incidence of cesarean sections in the State of Wisconsin was 2.02 per cent from 1934 to 1940, and rose to 3.11 per cent in 1947.

TABLE I. CESAREAN SECTIONS, 1933 TO 1947

	1933-1937	1938-1942	1943-1947
Total deliveries	3,854	5,482	10,554
Cesarean sections	287	384	560
Incidence	1 in 13	1 in 14	1 in 16
	7.4%	7%	5.4%

We consider an incidence of from 5 per cent to 5.5 per cent the irreducible minimum to which this operative treatment can be reduced under our present indications for cesarean sections. Andrews, Nichols, and Andrews[2] show an incidence of 10.5 per cent, of which 6.9 per cent were private and 3.6 per cent were referred patients. Thoms and Godfried[3] reported an incidence of 3.2 per cent in ward and 9.6 per cent in private cases at the New Haven Hospital in a ten-year survey. Irving[4] reported 1,887 consecutive sections at Boston Lying-in Hospital from 1934 to 1943 with an incidence of 3.12 per cent in ward cases and 6.7 per cent in private cases.

At Milwaukee Hospital from 1943 to 1947 there were 560 operations done by 19 operators, thirteen of whom were recognized specialists in obstetrics and gynecology. The remaining six were general practitioners who accounted for fourteen cases or 2.5 per cent of the total.

Types of Operation

The low cervical cesarean section has become the operation of choice in most cases, 92.5 per cent of the operations having been of this type during the last five-year period. Table II shows the marked increase in the incidence of this operation during the fifteen years, and the marked decrease in the classical type.

TABLE II. TYPES OF CESAREAN SECTIONS, 1933 TO 1947

	1933-1937	1938-1942	1943-1947
Classical	74 (25.8%)	25 (6.5%)	33 (5.8%)
Low cervical	174 (60.7%)	336 (87.5%)	517 (92.5%)
Cesarean hysterectomy	3 (1%)	5 (1.3%)	9 (1.5%)
Hirst	0	0	1 (0.2%)
Sellheim	9 (3.1%)	0	0
Type not given	27 (9.4%)	18 (4.7%)	0
Extraperitoneal	0	0	0

The extraperitoneal operation was not performed at this hospital. Our records indicate that it was unnecessary. There were no maternal deaths or severe infections during the last five years. Undoubtedly this view was not shared by clinics in which indigent and infected patients were more prevalent. Proper prenatal care and instruction can do much to prevent intrapartum or postpartum infection.

For the past five years it has been a routine procedure in all patients with ruptured membranes to instill into the vagina every four hours either a 5 per cent aqueous mercurochrome or 1:2,000 aqueous Zephiran solution. Patients admitted for elective cesarean section receive this treatment the night preceding and the morning of surgery. Penicillin and the sulfonamides are used prophylactically in potentially infected patients, and therapeutically in those showing signs of morbidity. The incidence of cesarean hysterectomies remained quite constant (1 per cent to 1.5 per cent). Conservatism was our aim in the management of both mother and child. This low incidence of cesarean hysterectomy would have been, much higher if severe infections had ensued in spite of the previously mentioned treatment.

TABLE III. CONDENSED INDICATIONS FOR CESAREAN SECTION

	1933-1937 (PER CENT)	1938-1942 (PER CENT)	1943-1947 (PER CENT)
Previous cesarean section	18.2	33.3	43.4
Contracted pelvis	27.5	17.9	10.8
Cephalopelvic disproportion	20.3	21.9	9.7
Placenta previa	7.3	3.9	7.0
Fulminating toxemia	8.0	7.6	6.0
Premature separation of placenta	3.2	3.9	4.7
Previous difficult deliveries	4.9	3.6	3.9
Previous surgery to birth canal	.7	1.3	4.2
Pelvic tumor	—	2.4	1.7
Abnormal presentation	—	2.1	2.8
Miscellaneous	9.9	2.1	5.8

Table III shows the indications for cesarean section. In tabulating the indications, the primary reason for the operation was recorded. In many cases there were two or three substantial indications, but we have used the most predominant cause. Where previous cesarean section was performed this was tabulated as the indication regardless of other conditions which might have been present such as abruptio placentae, toxemia, or other conditions. We practice the dictum of once a cesarean, always a cesarean, and our results prove the

efficacy of this procedure. There have been no ruptured uteri in any patients who have had a previous cesarean section, and no maternal deaths in the last 560 operations. Almost one-half, or 43.4 per cent, of this group were repeat sections. This high rate was due, in part, to our classification of indications for cesarean section.

While there has been a rise in the incidence of repeat cesarean sections, there has been a marked decrease in the incidence of operations done for cephalopelvic disproportion and contracted pelvis. The increased use and knowledge of x-ray pelvimetry have contributed considerably to this reduction.

The relative number of operations done because of placenta previa and premature separation of the placenta has remained quite stationary. While not all patients were submitted to cesarean section, we believe that unless conditions exist for rapid vaginal delivery, section should be performed.

Patients with pre-eclampsia or eclampsia were treated medically, and vaginal delivery was anticipated. No patients were considered operable in the convulsive state or immediately following convulsions. When pre-eclampsia was considered progressive in spite of all medical treatment, and eclampsia was unabatable, cesarean section was performed. Until better medical management is obtained, or until more successful methods of induction of labor are known, fulminating toxemias will probably continue to be the cause of from six to eight per cent of cesarean sections done in most communities. Patients having a cesarean section performed because of previous difficult deliveries were those who should have been sectioned primarily. Many of these patients presented histories of stillbirths following long and difficult labors. They then consulted a specialist in the hope of delivering a live child. The specialist performed a section many times because of this anxiety. The remaining indications require little comment. The Rh-negative mother with increasing antibodies is no longer an indication for cesarean section. The six instances of section done because of no progress following artificial rupture of membranes were the type of indications which we attempt to limit to a minimum.

Anesthesia

Table IV shows that general anesthesia was the anesthetic of choice in most instances at this hospital. All general anesthetics were given by competent nurse anesthetists using cyclopropane, nitrous oxide, Pentothal sodium, ethylene, and ether, in various combinations or separately. During the last five-year period there were only three cases of postoperative atelectasis, three upper respiratory infections, and one case of bronchopneumonia following inhalation anesthesia. The most satisfactory results were obtained for both mother and infant when competent nurse anesthetists used the agent which they themselves were best qualified to use. From 1943 through 1945 caudal anesthesia was used extensively. Since that time it has been discontinued because of two maternal deaths which occurred prior to vaginal delivery and which were attributable to the caudal anesthetic. In the last two years the use of spinal anesthesia has shown a relative increase. Local anesthesia has been reserved for patients in whom the other anesthetic agents were contraindicated for maternal or fetal reasons.

TABLE IV. TYPES OF ANESTHESIA

	1943	1944	1945	1946	1947
General	46	69	81	74	105
Caudal	37	42	25	0	6
Local	0	4	13	9	6
Spinal	0	0	0	5	20

Morbidity

During the last five-year period, 85 patients, or 15.2 per cent, showed a temperature rise to 100.4°F. or more some time during two twenty-four-hour periods exclusive of the first twenty-four hours. Table V shows the various causes of morbidity. The prophylactic and therapeutic use of penicillin and the sulfonamides in these patients was of inestimable value. The previously mentioned vaginal instillation of antiseptic solution, as well as improved nursing care, has been important in obtaining this low morbidity rate.

TABLE V. MORBIDITY

	1943-1947
Postoperative reaction and sapremia	30
Cystitis	12
Parametritis	10
Thrombophlebitis	6
Pyelonephritis	4
Pulmonary embolism	4
Wound infection	3
Upper respiratory infection	3
Postoperative ileus	3
Atelectasis	3
Mastitis	2
Bronchopneumonia	1
Rheumatic fever	1
Eclampsia	1
Mesenteric thrombosis	1
Sulfonamide reaction	1
Total	85
Morbidity rate	15.2%

Fetal Mortality

There were nine stillbirths associated with cesarean sections performed from 1943 through 1947, a rate of 1.6 per cent, and fourteen neonatal deaths, a rate of 2.5 per cent. Tables VI, VII, and VIII show the details in these cases. It was noteworthy that all of the neonatal deaths were among premature infants, nine of whom died of atelectasis during the first twenty-four hours. Three of the infants succumbed to erythroblastosis fetalis though the Rh factor was not the indication for section in any of these cases. With increasing knowledge of the Rh problem, these deaths may soon be preventable. The neonatal death rate for the entire fifteen-year period was 3.6 per cent, and the stillbirth rate, 1.95 per cent.

Maternal Mortality

During the entire fifteen-year period there were ten maternal deaths following cesarean section. It was significant that during the last five-year period, when nearly one-half, or 560 operations, were performed, there were no maternal deaths. Again, it was during this period that the previously mentioned treatment of antiseptic vaginal instillations and the use of antibiotics were utilized. This effect upon maternal mortality was striking. Table IX demonstrates the

TABLE VI. DEATHS FOLLOWING CESAREAN SECTION

	1933-1937	1938-1942	1943-1947
Cesarean sections	287	384	560
Maternal deaths	8 (2.8%)	2 (0.5%)	0
Stillbirths	5 (1.7%)	11 (2.8%)	9 (1.6%)
Neonatal deaths	14 (4.9%)	19 (4.9%)	14 (2.5%)

various causes of maternal deaths. The classical type of operation was performed in four and the low cervical flap in six cases.

TABLE VII. NEONATAL DEATHS* FOLLOWING CESAREAN SECTION, 1943 THROUGH 1947

CAUSES OF DEATH	NO.
Atelectasis, death within 24 hours	9
Erythroblastosis foetalis	3
Bronchopneumonia	2

*All infants were less than 5 pounds in weight.

TABLE VIII. NEONATAL DEATHS FOLLOWING CESAREAN SECTION, 1943 THROUGH 1947

INDICATION FOR SECTION	NO.
Placenta previa	4
Pre-eclampsia	4
Premature separation of placenta	2
Large fibromyoma with ruptured membranes and shoulder presentation	1
Previous amputation of cervix with premature rupture of membranes	1
Premature labor. Old third degree perineal laceration with three previous attempts at repair	1
Elderly primipara with previous extensive cautery of cervix. Test of labor without progress for 16 hours	1
Total	14

TABLE IX. MATERNAL DEATHS FOLLOWING CESAREAN SECTION, 1933 THROUGH 1942

Puerperal sepsis with terminal bronchopneumonia	5
Postoperative bronchopneumonia	1
Uterine apoplexy. Postpartum hemorrhage	1
Postoperative shock	1
Secondary granulopenia with bronchopneumonia	1
Malignant hypertension. Uremia	1
Total	10
Death rate	0.81%

Summary

1. An analysis of 1,231 consecutive cesarean sections performed at Milwaukee Hospital from 1933 through 1947 has been presented.

2. The cases were divided into three five-year periods, showing the trends in present-day cesarean sections.

3. The total incidence of cesarean section was 6 per cent, with a maternal mortality rate of 0.81 per cent, neonatal death rate of 3.6 per cent, and stillbirth rate of 1.95 per cent.

4. No maternal deaths occurred during the last five-year period when approximately one-half (560) of the operations were performed.

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RUPTURE OF THE PREGNANT UTERUS

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RUPTURE of the uterus is a most dangerous complication of pregnancy and labor. This fact has been emphasized in more than thirty articles on this subject which have appeared in the American medical literature in the past ten years. Table I represents a summary of the findings of those authors who have reported large series in that interval.

TABLE I. RUPTURE OF THE PREGNANT UTERUS

AUTHOR	PERIOD	NO. OF DELIVERIES	RUPTURES		SPONTANEOUS		DUE TO CESAREAN SCAR		DUE TO OTHER CAUSES		OBSTETRICAL TRAUMA	
			NO.	INCIDENCE	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Sheldon[1]	1918-34	47,554	26	1:1,829	9	34.6	5	19.2	4	15.3	17	65.4
Lynch[2]	1920-45	41,706	44	1:1,118	17	38.6	11	25	6	13.6	27	61.3
Morrison and Douglas[3]	1920-43	65,916	45	1:1,465	22	48.8	17	37.7	5	11.1	23	51.2
Delfs and Eastman[4]	1920-45	53,574	53	1:1,010	27	50.9	10	18.8	17	32.1	26	49.1
Acken[5]	1924-39	25,935	15	1:1,729	10	66.6	8	53.3	2	13.3	5	33.3
Bill, Barney, and Melody[6]	1925-41	69,391	23	1:2,756	15	65.2	13	56.5	2	8.7	8	34.7
Dugger[7]	1931-41	318,103	105	1:3,029	60	57.4	34	32.2	26	25.1	45	42.6
Present study	1932-46	111,753	57	1:1,961	47	82.4	26	45.6	21	36.8	10	17.6

The reports have been arranged in chronological order and each report analyzed to indicate the incidence of rupture of the uterus in each series. The ruptures have been classified, etiologically, as either spontaneous or due to obstetrical trauma, and the former classification divided into two subclasses, namely, spontaneous ruptures through the scars of previous cesarean sections and spontaneous ruptures due to other causes.

Review of Table I reveals some interesting trends. Dugger's[7] report covering the findings at thirty-one hospitals in Philadelphia County, Pennsylvania, indicated a considerable reduction in the incidence of ruptures of the uterus, when compared with the statistics of previous investigators. This trend was not found in the present study, where the incidence of one rupture in every 1,961 deliveries did not differ appreciably from the incidence reported by Sheldon[1] at the Boston Lying-in Hospital between 1918 and 1934. Study of the next four columns indicates definite trends for there was an increase in the incidence of spontaneous ruptures from a low of 34.6 per cent in Sheldon's[1] report to a high of 82.4 per cent in this report, and a decrease in the incidence of ruptures due to obstetrical trauma to the low point of 17.6 per cent reported in this study. The decrease in the latter category, indicating an improvement in the art of obstetrics, as it is practiced today, is most gratifying to both the practitioners and the teachers of obstetrics. The increase in the former category can be explained in part by the increase in the incidence of ruptures of the scars of previous cesarean sections. The figure 45.6 per cent found in the present study is

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considerably higher than the figures reported by Sheldon[1] and Lynch[2] and Delfs and Eastman,[4] slightly higher than those of Morrison and Douglas[3] and Dugger[7] but somewhat less than those of Acken[5] and Bill, Barney, and Melody.[6] It is difficult to understand why the incidence of spontaneous ruptures of the uterus due to other causes is higher in this report than in any previous study, for the figure of 36.8 per cent has been approximated only by Delfs and Eastman.[4]

When this review was initiated at Bellevue Hospital, it was decided to limit the collected cases to the fifteen-year interval from 1932 to 1946 in order to present the problem as it occurs in present-day obstetrical practice. When the interval was limited in this way a sufficient number of cases could not be collected at Bellevue Hospital alone. For this reason, four additional large hospitals in the metropolitan area were included, namely, the Sloane Hospital for Women, St. Vincent's, Kings County, and Lincoln Hospitals. Between 1932 and 1946, at the five institutions, there were fifty-seven ruptures of the uterus in a total of 111,753 consecutive deliveries, the diagnosis in each instance being confirmed by operation, autopsy, or postmortem vaginal examination.

The three groups, namely, spontaneous ruptures of the uterus due to the scars of previous cesarean sections, spontaneous ruptures due to other causes, and ruptures due to obstetrical trauma will be separately analyzed to determine the causative and objective findings important to early diagnosis and treatment. A few cases in each category will be briefly summarized to illustrate the more important points.

Spontaneous Rupture Due to Cesarean Scars

Between 1932 and 1947, at Bellevue Hospital, there were 246 patients who carried pregnancies to the last trimester after a previous cesarean section. Study of their case records reveals the findings outlined in Table II.

Table II. Incidence of Cesarean Scar Rupture

	NO.	PER CENT
Pregnancies subsequent to cesarean section	246	100.0
Total ruptured uteri	7	2.8
Scars of unknown type	53	21.6
Classical scars	77	31.3
Estimated total classical scars	94	38.2
Ruptures of classical scars	4	4.2
Lower segment scars	116	47.1
Estimated total lower segment scars	152	61.8
Ruptures of Lower segment scars	3	1.9

There were seven ruptures of the uterus, an incidence of 2.8 per cent. Since in 53, or 21.6 per cent, of the patients the type of cesarean section previously performed was not known, the total number of classical and lower segment scars had to be estimated. There were four ruptures in an estimated total of 94 classical scars, an incidence of 4.2 per cent, and three ruptures in an estimated total of 152 lower segment scars, an incidence of 1.9 per cent. From these figures it could be concluded that classical scars were more than twice as likely to rupture as lower segment scars but the necessity to compute an estimated rather than an actual total of both types of scars colors the validity of this conclusion.

Table III is an analysis of the twenty-six cases of rupture of the scars of previous cesarean sections, collected from five hospitals.

Nineteen, or 73 per cent, of these ruptures were through the scars of previous classical sections and only seven, or 27 per cent, through lower segment scars, a ratio of 2.7 to 1. There were three ruptures of transverse lower segment scars and four ruptures of longitudinal lower segment scars. All the ruptures occurred after the twenty-fourth week of gestation, two, or 8 per cent, before the

twenty-eighth week, three, or 11 per cent, between the thirty-second and the thirty-sixth weeks, and twenty-one, or 81 per cent, in the last four weeks of gestation. Sixty-one per cent of the patients were in labor at the time of rupture. Pain and abdominal tenderness were the most dependable findings, occurring in 88 per cent of the patients observed. Shock occurred in 34 per cent and cessation of labor in 32 per cent of those in labor at the time of rupture. In each instance that labor ceased, the infant was found free in the abdominal cavity. External bleeding was the least dependable finding, occurring in only 19 per cent.

TABLE III. ANALYSIS OF CESAREAN SCAR RUPTURES. TOTAL NUMBER, TWENTY-SIX

		NO.	PER CENT
1. *Type of Scar:*			
	Classical	19	73
	Lower segment	7	27
	Lower segment transverse	3	
	Lower segment longitudinal	4	
2. *Time of Onset:*			
	Week 36 to 40	21	81
	Week 32 to 36	3	11
	Week 28 to 32	00	
	Week 24 to 28	2	8
	Labor	16	61
3. *Clinical Picture:*			
	Pain	23	88
	Abdominal tenderness	23	88
	Shock	9	34
	Cessation labor	5	32
	External bleeding	5	19
4. *Treatment:*			
	Hysterectomy	15	
	Repair	10	
	Untreated	1	
5. *Mortality:*			
	Maternal	1	3.8
	Infant	12	46.0

In fifteen instances a supravaginal hysterectomy was performed and in ten instances the uterine rupture was repaired. Five of the latter patients were sterilized by the Pomeroy technique. They all recovered and there was no appreciable difference in morbidity between the cases treated by hysterectomy and those in which the uterine rupture was repaired. Obviously, there is danger of the occurrence of a similar accident in subsequent pregnancies when the uterine rupture is repaired without ligation of the Fallopian tubes. No record of subsequent pregnancies was available for these patients but Pettit[8] and Leech[9] have each reported a case of repeated rupture of the uterus. The maternal mortality was 3.8 per cent and the infant mortality was 46 per cent.

There were seven cases of complete rupture of the uterus in which the infant, the placenta, or both were found free in the abdominal cavity. The following case report is typical of four of these cases.

CASE 1.—G. M. was a 30-year-old, white multipara with a history of three spontaneous deliveries prior to 1936, a classical cesarean section for placenta previa in 1937 and a subsequent spontaneous delivery in 1941. She was admitted at term, on Oct. 28, 1942, complaining of mild labor pains of three hours' duration which had ceased one hour prior to admission and had been replaced by severe abdominal pain. The patient was in shock on admission and the baby could be felt easily through the abdominal wall. She was transfused and operated upon two hours after admission. A dead baby was found free in the peritoneal cavity and an incompletely separated placenta protruded through the ruptured

uterine scar. There were 2,000 c.c. of fresh blood and clots in the peritoneal cavity. The patient made an uneventful recovery after a supravaginal hysterectomy.

Two cases presented no symptoms or signs of shock in spite of a complete uterine rupture with the baby and placenta free in the peritoneal cavity. In each case the uterus had clamped down following the extrusion of the products of conception. One of these case reports follows.

CASE 2.—A. S. was a 27-year-old, white multipara with an ample pelvis, a ten-year history of treated diabetes, and three previous low classical cesarean sections, in 1936, 1937, and 1938, respectively. The first child, a 10 pound breech presentation, expired with pneumonia at the age of five months, the second, weighing 9½ pounds on delivery, is now living, and the third was a 10 pound stillbirth. Her present pregnancy, as observed in the antepartum clinic, was uneventful, the diabetes being well controlled on 65 units of insulin daily. She was admitted on Dec. 5, 1939, in her thirty-sixth week of gestation for an elective section. The fetus was presenting as a breech and its weight was estimated at about 6½ pounds. On admission she did not complain of abdominal pain and the scar was not tender. Thirteen hours after admission the patient had a few irregular uterine contractions over a period of two hours. The fetal heartbeat was lost and the infant was palpated in the transverse position. The patient did not complain of pain, the abdomen was not tender, the pulse was 88 and the blood pressure was 130/75. Seven hours later she complained of right upper quadrant discomfort and pain in the right scapula region. There was moderate tenderness but no spasm in the right upper quadrant. Four hours later the pain was more severe and more generalized and there was definite lower abdominal tenderness. The pulse and blood pressure were still normal. She was taken to the operating room and a 6 pound baby, the placenta, and 300 c.c. of blood were found in the peritoneal cavity. There was an 8 cm. tear in the anterior surface of the lower half of the body of the uterus, the uterus was well contracted and there was no fresh bleeding. A supracervical hysterectomy was done and the patient made an uneventful recovery. The infant was stillborn.

One uterus apparently ruptured in the operating room during the induction of anesthesia. There were no prior symptoms or signs of the impending rupture and a stillborn infant, the placenta, and 1,500 c.c. of blood were found in the peritoneal cavity. The patient made an uneventful recovery following a supravaginal hysterectomy and a 2,000 c.c. transfusion.

Three patients, with incomplete uterine ruptures, continued in labor and delivered vaginally. Their case reports are as follows:

CASE 3.—B. D. The patient was a 36-year-old, white multipara with a history of twelve normal, spontaneous deliveries and a classical cesarean section on Feb. 7, 1943, for premature separation of the placenta. Her prenatal course was uneventful and she was admitted in labor, at term, on July 2, 1945. It was decided to permit labor under close supervision. She complained of abdominal pain throughout labor but the scar was not tender. After a twelve-hour labor she was delivered by low forceps of a live infant and the placenta was delivered by a modified Credé maneuver. The uterus contracted well, the blood loss was estimated to be 150 c.c. and the pulse and blood pressure were recorded to be normal. The uterine cavity was not manually explored. Twelve hours post partum abdominal distention appeared and a diagnosis of ruptured uterus was made. At operation a 10 cm. rent through the old scar was found and there were 250 c.c. of blood in the peritoneal cavity. The patient made an uneventful recovery after a supravaginal hysterectomy.

CASE 4.—E. C. was a 42-year-old, white multipara with a history of five previous normal, spontaneous deliveries and a classical cesarean section for an unknown indication in 1930. She was not observed during her antepartum course. She was brought to the hospital by ambulance on Oct. 10, 1933, at term, after being in labor at home for seven hours and

complaining of severe abdominal pain of one hour's duration. On admission she was in active labor but in deep shock with a pulse of 180. She delivered a stillborn infant twenty minutes after admission and expired ten minutes later. Postmortem vaginal examination disclosed a midline, anterior, uterine rupture extending from the cervix to the apex of the fundus uteri.

CASE 5.—S. O. The patient was a 27-year-old, white multipara with a history of the spontaneous delivery of a living 7 pound, 3 ounce infant in 1942 after a seven-hour labor and a low-flap cesarean section, after a six-hour labor, in 1945, for premature separation of the placenta, with the delivery of a 5 pound, 12 ounce stillbirth. The uterus was packed and her postoperative course was febrile for several days. She was admitted for observation, at term, on May 30, 1947, had twelve hours of false labor on June 4, and began active labor on June 6. Since the vertex was fixed in the pelvis and the cervix soft, retracted, and one finger dilated, it was decided to allow her to go through labor. The scar was not tender. After one and one-half hours of labor she complained of constant lower abdominal pain, two hours later the scar was tender, and forty-five minutes later a defect was palpable in the lower uterine segment. Labor continued, the vertex was well engaged, the cervix three fingers dilated, and the pulse and blood pressure remained normal. After a five and one-half-hour labor she was delivered by suprafundal pressure of a living 8 pound, 7 ounce infant, the placenta, and 400 c.c. of blood. The uterus was manually explored immediately and an anterior rupture of the lower uterine segment identified. A transfusion of 1,000 c.c. of blood was started and a laparotomy performed thirty minutes later, disclosing an 8 cm. tear through the previous scar, 300 c.c. of free blood and a dissecting hematoma covering half the corpus and infiltrating both broad ligaments. The patient made an uneventful recovery after a supravaginal hysterectomy.

The remaining sixteen cases were all incomplete uterine ruptures with the infant still in utero and varying degrees of separation of the scar present. In two instances the separation of the scar was found at operation with no prior symptoms or physical findings. The following case report is typical of the fourteen remaining cases.

CASE 6.—C. A. The patient was a 22-year-old, white multipara with a history of two previous classical cesarean sections, the first in 1932 after a four-hour trial labor and the second, in 1934, an elective section, before the onset of labor. She was admitted on May 23, 1936, in her thirty-ninth week of gestation complaining of moderate abdominal discomfort. The uterine scar was tender. At operation an 8 by 10 cm. window was found at the site of the previous scar. A 6 pound, 7 ounce boy in good condition was delivered, the uterine wound repaired, a Pomeroy sterilization performed, and the patient made an uneventful recovery.

Spontaneous Ruptures Due to Other Causes

This group of cases, numbering twenty-one, or 37 per cent of the total, ranks second in the order of frequency and possesses the highest maternal mortality, 47.6 per cent. This is an interesting group for in most instances the uterine rupture was completely unexpected, frequently misdiagnosed or diagnosed too late, and in twelve instances the cause was not found at either operation or autopsy. The twenty-one cases have been analyzed in Table IV.

The site of rupture was in the lower uterine segment alone in ten, or 48 per cent, of the cases and had extended from the lower uterine segment into the corpus in an additional six cases. The corpus alone was involved in only five or 24 per cent. The rupture occurred during labor, at term, in eighteen, or 85 per cent, and only three patients were not in labor at the time of rupture.

There were twelve cases in which no adequate causative factor could be found. Eight of these patients could be classified as grand multiparas, each

TABLE IV. ANALYSIS OF SPONTANEOUS RUPTURES DUE TO CAUSES OTHER THAN PREVIOUS CESAREAN SECTIONS

	NO.	PER CENT
1. *Site of Rupture:*		
Lower segment	16	76
Lower segment alone	10	48
Lower segment and corpus	6	28
Corpus alone	5	24
2. *Time of Rupture:*		
Labor at term	18	85
Pregnancy, not in labor	3	15
3. *Cause of Rupture:*		
Multiparity	8	38
Unknown	4	19
Corpus scar	3	14
Myomectomy scar	1	4.8
Cervical scar	1	4.8
Large baby	1	4.8
Low implantation of placenta	1	4.8
Hydrocephalus	1	4.8
Adenomyosis	1	4.8
4. *Clinical Picture:*		
Shock	21	100
Abdominal pain	17	81
Abdominal tenderness	16	76
Cessation of labor	14	77
External bleeding	8	38
5. *Mortality:*		
Maternal	10	47.6
Infant	18	85.7

patient having had at least six previous full-term pregnancies terminating in spontaneous deliveries. In four cases, however, even this possible predisposing cause was absent. In three cases the rupture occurred in an area of scar tissue which was demonstrable both grossly and microscopically. Two of these patients had histories of a previous septic abortion and although a similar history was suspected in the third case it was not proved. The rupture of the myomectomy scar was included in this classification for purposes of statistical analysis and for comparison with the findings of previous investigators, instead of in the cesarean scar group where it rightfully belongs. One rupture originated in a scarred cervix and extended into the lower uterine segment, one occurred in the first stage of labor with a 12 pound baby, one in a precipitate labor in the presence of a low implantation of the placenta, one in the delivery of a hydrocephalic baby, and the last, due to adenomyosis, was reported completely by Stone[10] in 1938.

The clinical picture of these twenty-one patients included signs and symptoms of shock in 100 per cent, abdominal pain in 81 per cent, abdominal tenderness in 76 per cent, cessation of labor in 77 per cent of those in labor at the

TABLE V. TREATMENT OF SPONTANEOUS RUPTURES DUE TO CAUSES OTHER THAN PREVIOUS CESAREAN SECTIONS

			MORTALITY			
			MATERNAL		INFANT	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Abdominal delivery and hysterectomy	12	57.1	4	33.3	11	91.6
Vaginal delivery and hysterectomy	3	14.3	1	33.3	2	66.6
Vaginal delivery, no hysterectomy	3	14.3	3	100.0	2	66.6
Undelivered, not operated upon	2	9.5	2	100.0	2	100.0
Abdominal delivery and repair of rupture	1	4.8	0	0	1	100.0

time of rupture, and external bleeding in 38 per cent. The maternal mortality was 47.6 per cent and the fetal mortality 85.7 per cent. Table V summarizes the maternal and infant mortality according to the type of treatment.

The maternal mortality was 33.3 per cent in the twelve cases treated by abdominal delivery and hysterectomy, in ten of which the fetus and placenta were found in the peritoneal cavity at operation. The case reports of two of these patients follow.

CASE 7.—H. M. The patient was a 28-year-old white multipara with a history of two previous normal pregnancies terminating in spontaneous deliveries of a 7 pound and a 10 pound infant at home. She did not attend prenatal clinic. The membranes ruptured spontaneously at term and after a seven-hour labor the uterine contractions ceased, continuous lower abdominal pain appeared and vaginal bleeding of approximately 150 c.c. occurred. She was admitted to the hospital as an emergency case. Temperature was 99.6° F., pulse 130, blood pressure 120/80. There was no active vaginal bleeding but the infant could be easily felt through the abdominal wall and the uterus was separately palpable. The patient was transfused and a laparotomy was performed three hours after admission. At operation a transverse laceration was found in the lower uterine segment and a stillborn 9 pound, 12 ounce female infant, the placenta, and 100 c.c. of blood were found free in the abdominal cavity. A supravaginal hysterectomy was performed. Five grams of sulfanilamide were placed under the bladder flap and 5 grams in the peritoneal cavity. Penicillin was administered for four days postoperatively and the patient made an uneventful recovery.

CASE 8.—M. J. The patient was a 28-year-old multipara with a history of six previous spontaneous deliveries who was admitted at term on Oct. 11, 1945, as an emergency case, having had no prenatal care. She had been in labor for eleven hours at home and one hour prior to admission labor had ceased and she complained of severe abdominal pain. There had been no vaginal bleeding. On admission she was in deep shock, the infant could be easily felt through the abdominal wall, and no fetal heartbeat could be heard. Five hundred c.c. of plasma and 500 c.c. of blood were administered immediately and a laparotomy was performed two and three-fourths hours after admission. At operation a rent was found in the lower uterine segment extending into the left broad ligament. An 8 pound, 12 ounce stillborn infant and considerable free blood were found in the peritoneal cavity and a massive hematoma in the left broad ligament. A supravaginal hysterectomy was performed, and a second transfusion of 500 c.c. administered, but the patient succumbed eight hours postoperatively, never having recovered from shock.

The maternal mortality was 33.3 per cent in the three patients delivered vaginally and treated by supravaginal hysterectomy. Two of the case histories are as follows:

CASE 9.—A. B. was a 26-year-old primipara with an ample pelvis and a normal prenatal course who was admitted at term, in labor, on April 10, 1935. After twelve hours of desultory labor and seven hours of strong labor with the membranes intact, the vertex was in the right occipitoposterior position at the spines and the cervix was three fingers dilated. One hour later the cervix was fully dilated, the vertex was in the right occipitotransverse position 2 cm. below the spines and the membranes were ruptured artificially. Moderate vaginal bleeding was noted, labor ceased, and the fetal heartbeat was lost. The patient was in good condition, the pulse 104 and strong, and the blood pressure was 118/84. After a five and one-half hour second stage the uterus was tense and tender and after a seven and one-half-hour second stage a 6 pound, 11 ounce stillborn female infant was easily delivered by low mid-Barton forceps. The placenta was retained but no unusual vaginal bleeding occurred and the patient remained in good condition. After a sixty-minute third stage the placenta was manually removed and a cervical laceration extending into the right anterior wall of the lower uterine segment was identified. The patient's condition remained good and at laparotomy the uterine rupture was found to be confined to the lower uterine segment dissecting across but not through the right uterine artery. A supra-

vaginal hysterectomy was performed and the lacerated cervix was repaired. The patient had a morbid postoperative course but was discharged well on the thirty-first postoperative day.

CASE 10.—M. H. The patient was a 32-year-old multipara with a history of seven previous spontaneous deliveries, who delivered a 6 pound, 3 ounce living female infant after a two-hour labor, forty-eight hours after the membranes had ruptured spontaneously. The placenta delivered spontaneously. Three hours after delivery, vaginal hemorrhage was noted and vaginal examination disclosed a cervical laceration extending into the right broad ligament. A transfusion was started and a supravaginal hysterectomy was performed three hours later but the patient succumbed on the operating table.

The maternal mortality of the three cases delivered vaginally and not treated by hysterectomy was 100 per cent. One of the case histories follows.

CASE 11.—C. H. The patient was a 31-year-old Negro multipara, with a history of six previous spontaneous deliveries, admitted on Jan. 21, 1946, complaining of one episode of bright red vaginal bleeding of one hour's duration in her twenty-seventh week of gestation. She was observed for seven days but had no further vaginal bleeding. On Jan. 28, 1946, after a two-hour labor the patient precipitated a 4 pound, 8 ounce premature infant in good condition. This was followed by moderate vaginal bleeding. Fifteen minutes later the placenta was spontaneously delivered. Following the third stage the bleeding became more profuse. The uterus and vagina were manually explored and firmly packed and a transfusion started, a total of 1,000 c.c. of blood and 500 c.c. of plasma being administered. When the patient bled through the packing, it was removed, the uterus and vagina reexplored and repacked. The patient expired three hours after delivery. Postmortem examination disclosed a 3 cm. rupture of the anterior wall of the lower uterine segment containing a large vein.

The maternal mortality for the two undelivered patients not operated upon was 100 per cent. Both catastrophes were dramatically sudden. The case history of one follows.

CASE 12.—V. D. The patient was a 40-year-old multipara with a history of eight previous spontaneous deliveries who was admitted in good labor, at term, with ruptured membranes. While she was being admitted a strong uterine contraction was palpated, following which labor stopped, the patient complained of abdominal pain, the fetal heartbeat was lost, the infant could be easily felt, and the patient went into profound shock. She expired three hours later while receiving a transfusion. Postmortem examination disclosed an average-sized infant and 4,000 c.c. of blood in the peritoneal cavity. The cervix was three fingers dilated. There was a rupture of the uterus extending from the lower uterine segment, through the right uterine artery to the right cornu.

One patient recovered following abdominal delivery of a stillborn infant and surgical repair of a rupture of the left lateral wall of the lower uterine segment.

CASE 13.—A. P. The patient was a 34-year-old white multipara with a history of the spontaneous delivery of a 7 pound, 8 ounce child in 1928 and three spontaneous early abortions in 1930, 1940, and 1944. She was admitted Nov. 15, 1945, at term, after an uneventful prenatal course. On admission an average-sized infant was in the left occipitoposterior position with the vertex unengaged. The membranes were intact, the cervix was one finger dilated and the patient was in early labor. After thirteen hours of mild labor the uterine contractions ceased and the patient complained of moderate, continuous abdominal pain. Four hours later moderate vaginal bleeding and generalized abdominal tenderness were noted. The patient was in shock and a diagnosis of abruptio placentae was made. The fetal heart could not be heard. The patient was transfused and a laparotomy performed. A dead baby and the placenta were found free in the abdominal cavity and there was a rupture of the left

lateral wall of the corpus uteri extending from the fundus into the broad ligament. The uterus was repaired in layers and the abdomen closed. The patient developed a left parametritis and signed herself out of the hospital on her eleventh day post partum although she was still febrile.

Rupture of the Uterus Due to Obstetrical Trauma

It was gratifying to discover that only ten ruptures of the uterus of this type occurred in this series, representing an incidence of only one case in every 11,175 deliveries. The ten cases have been summarized in Table VI.

TABLE VI. ANALYSIS OF TRAUMATIC RUPTURES. TOTAL NUMBER, TEN

	NO.		PER CENT	
1. *Cause of Rupture:*				
Version and breech extraction	4		40	
Breech extraction	3		30	
Forceps	2		20	
Unknown	1		10	
2. *Clinical Picture:*				
External bleeding	8		80	
Shock	8		80	
Abdominal pain	3		30	
Abdominal tenderness	2		20	
3. *Site of Rupture:*				
Lower segment	10		100	
Lower segment alone		7		70
Lower segment and corpus		3		30
4. *Mortality:*				
Maternal	8		80	
Infant	8		80	

Four of these catastrophes occurred in the course of versions and breech extractions, performed in three instances for transverse presentations and in one instance for a prolapsed cord. In the four cases the rupture occurred, apparently, in the process of the breech extraction, which was performed in three cases in spite of an incompletely dilated cervix and in one case in spite of a contraction ring. Two of these cases will be briefly summarized.

CASE 14.—N. B. The patient was a 24-year-old multipara admitted on March 20, 1945, in early labor. The membranes ruptured spontaneously after a four-hour labor and the cord prolapsed. Sterile pelvic examination showed the vertex to be presenting, not engaged, and the cervix fully dilated with a contraction ring palpable. Under deep anesthesia the contraction ring relaxed and an internal version was done, the vertex being converted to a double footling. Following the version, the contraction ring was again felt about the buttocks. The patient was given 1 c.c. of adrenalin and the anesthesia deepened. Eight minutes later the ring was felt to be soft. The breech was extracted easily and the shoulders with difficulty. The head was easily delivered by the Mauriceau-Smellie-Veit maneuver but during the delivery of the head it was believed that something "gave." The infant, a 7 pound, 5 ounce girl, was in good condition. The placenta was delivered by modified Credé maneuver, followed by moderately profuse vaginal bleeding. The uterine cavity was immediately explored and a defect in the posterior wall of the lower uterine segment was palpated. The uterine cavity was tightly packed, a transfusion started and the operating room made ready. A laparotomy was performed one hour after delivery and a 10 cm. laceration found in the posterior wall of the lower uterine segment. The patient made an uneventful recovery after a supravaginal hysterectomy.

CASE 15.—V. G. The patient was a 20-year-old multipara admitted in early labor on Sept. 13, 1934, in her thirty-fourth week of gestation with membranes ruptured, a transverse presentation, the fetal heart normal, and the cervix two fingers dilated. A No. 4

bag was inserted which was expelled eight hours later, when the cervix was found to be four-fingers dilated. A Braxton Hicks version was attempted unsuccessfully and a No. 5 bag was inserted with a 4 pound weight attached. The No. 5 bag fell out and was replaced three hours later. After a total of thirty-two hours the patient's temperature reached 103° F. and the cervix was four fingers dilated. A version and breech extraction were performed with great difficulty during the course of which the patient had a 400 c.c. hemorrhage. The placenta was expressed intact. Following the third stage the patient had another brisk hemorrhage and went rapidly into deep shock. A cervical laceration on the left side was sutured but the lower uterine segment was not manually explored. The patient was transfused and the uterine cavity packed. She received a total of 1,400 c.c. of blood, but bled through the packing and expired three hours after delivery. Postmortem examination disclosed that the cervical laceration extended into the left broad ligament.

Three of these four cases terminated fatally because of faulty obstetrical judgment, failure to determine the extent of the injury to the maternal soft parts and to adopt proper remedial procedures.

Three cases terminated fatally following breech extractions. Their case records will be briefly summarized.

CASE 16.—H. W. The patient was a 35-year-old multipara with a history of six previous spontaneous deliveries, the largest child weighing 8½ pounds at birth. She was admitted in early labor with a large infant in the right sacroposterior position and with the membranes ruptured. The fetal heartbeat was lost after a six-hour first stage. After a one-hour second stage, with the breech presenting two fingers below the spines, the frank breech presentation was easily broken up and extracted, the shoulders delivered by the Potter maneuver and the head delivered by the Wigand maneuver and an 8 pound, 3 ounce stillborn female infant delivered. The placenta was delivered by a modified Credé maneuver after a four-minute third stage with a total blood loss of 250 c.c. The lower uterine segment was not explored, the patient was not bleeding, and the delivery was believed to be an uncomplicated breech extraction. One-half hour after delivery profuse vaginal bleeding occurred, the patient went rapidly into profound shock and died thirty minutes later, one hour after delivery. Postmortem examination revealed a cervical laceration at 3 o'clock extending upward into the lower uterine segment and communicating with the peritoneal cavity.

CASE 17.—P. H. The patient was a 26-year-old primipara with an ample pelvis admitted at term on May 1, 1935. After an uncomplicated labor a 7 pound, 12 ounce stillborn female infant was delivered as an assisted breech from the left sacroanterior position by a Wigand-Martin maneuver. There was no vaginal bleeding, the placenta was delivered by a modified Credé maneuver, and no postpartum vaginal examination was done. The patient developed a generalized peritonitis and died on the fifth postpartum day. Postmortem examination revealed a rupture of the lower uterine segment and generalized peritonitis. There was no blood in the peritoneal cavity.

CASE 18.—C. M. The patient was a 30-year-old multipara admitted on June 8, 1937, in her thirty-second week of gestation, with a slight amount of painless bleeding and a left sacrotransverse position. After two days' observation the membranes ruptured spontaneously, the patient did not bleed further, and began labor four days later. No fetal heartbeat was heard at any time. After a twenty-five-hour labor the temperature rose to 101° F. A pelvic examination was done, the cervix was found to be three fingers dilated and a marginal placenta previa was felt. The cervix was manually dilated to four and one-half fingers and a small macerated stillbirth was easily extracted. The placenta was manually removed and because of persistent bleeding the uterus was packed. No lacerations of the cervix or lower uterine segment were described. One and one-half hours after delivery the patient bled through the packing and went into profound shock. A transfusion was started, the packing removed and the cervix palpated. A cervical laceration on the right side extend-

ing into the lower uterine segment was found. A total of 1,500 c.c. of blood was given by transfusion and the laceration repaired vaginally. The patient expired three and three-fourth hours after delivery.

There were two ruptures of the uterus due to the use of forceps. One patient, a multipara, expired, undelivered, three hours after an attempted forceps delivery through a four-finger cervix. Postmortem examination disclosed a rupture of the lower uterine segment with a hemoperitoneum. The second case will be summarized.

CASE 19.—G. G. The patient was a 22-year-old Negro multipara, with a small gynecoid pelvis with midpelvic contracture, with a history of the forceps delivery of a 6 pound, 14½ ounce male child in 1943. Her prenatal course was normal. She was admitted, at term, on Aug. 13, 1945, in early labor. After three hours of labor the fetal heartbeat fell to 90. Sterile vaginal examination disclosed that the cervix was three fingers dilated, the membranes intact, and the vertex in the right occipitoposterior position at the spines. The membranes were ruptured artificially and one hour later the cervix was fully dilated. After a forty-minute second stage the vertex was one finger below the spines in the right occipitoposterior position and the fetal heart rate was 70. The patient was anesthetized, prepared and draped, and a manual rotation attempted unsuccessfully. Kielland forceps were applied to the vertex below the spines and the vertex rotated anteriorly above the spines. After difficult traction a living 6 pound, 12 ounce child was delivered with the cord looped around the shoulder. The placenta was successfully delivered but because of continued vaginal bleeding the cervix was inspected and bilateral cervical lacerations identified and repaired. Two transfusions were administered. Two hours later a suprapubic mass was noted, another transfusion was administered, and three and one-half hours later, six hours after delivery, laparotomy disclosed a 5 cm. rupture of the lower uterine segment, a continuation of the cervical laceration. At this time the pulse was barely perceptible and the blood pressure was unobtainable. A supravaginal hysterectomy was performed and the pulse and blood pressure slowly rose to normal eight hours postoperatively, after two additional transfusions. Postoperatively the patient exhibited temporary mental confusion, kidney shutdown, and right leg paresis, and permanent occlusion of the central artery of the left retina.

One case was classified as due to trauma of an unknown nature. The patient was a 21-year-old multipara with a history of one previous normal pregnancy and delivery, who was admitted in her twenty-fourth week of gestation with a generalized peritonitis. At laparotomy the baby and placenta were found free in the abdominal cavity, having entered it through a rupture in the lower uterine segment. Although it was not proved, it was suspected that the uterus had been perforated in an attempted induction of labor by a midwife.

As can be seen in Table VI and in the cases summarized, external bleeding and shock are the most prominent symptoms in this type of rupture of the uterus, occurring in eight of the ten patients in this series, whereas abdominal pain and tenderness were less frequent. The lower uterine segment was involved in all cases. In three cases, the rupture extended from the lower segment into the corpus. The maternal and infant mortality was 80 per cent.

Summary and Conclusions

1. In present-day hospital obstetrical practice, rupture of the pregnant uterus occurs about once in every 2,000 deliveries. Approximately one-half of these will be ruptures of the scars of previous cesarean sections, one-third spontaneous ruptures due to other causes, and one-fifth due to the trauma associated with obstetrical interference.

2. Approximately 3 per cent of cesarean scars will rupture in subsequent pregnancies and classical scars are more than twice as likely to rupture as lower-segment scars. This can occur as early as the beginning of the third trimester but the peak incidence occurs in the last four weeks of pregnancy. Such patients, therefore, must have close supervision throughout this period, with speedy operative intervention upon the appearance of unusual abdominal pain or tenderness. Both repair of the scar and hysterectomy give equally good results and the procedure followed will depend upon the extent of the rupture. Obviously, hysterectomy removes the danger of a similar accident in subsequent pregnancies.

3. Spontaneous ruptures, not related to an old uterine scar, are second in the order of frequency. The lower uterine segment is involved in three-fourths of the cases and in two-thirds there is no history of previous operative procedures or abnormality of presentation which would suggest the imminence of this obstetrical catastrophe. Pain and abdominal tenderness are the earliest findings but are difficult to evaluate in a patient in active labor. In this series, the diagnosis was not suspected until signs and symptoms of shock supervened in 100 per cent of the cases. When the patient is undelivered, immediate laparotomy is indicated. If the patient is delivered vaginally external hemorrhage and shock are the most prominent findings. In most instances thorough manual examination of the cervix, lower uterine segment, and corpus will establish the diagnosis. In some instances, as in Case 11, a rupture can be missed in spite of this precaution. In such cases the uterus should be carefully packed and the operating room personnel alerted. If the patient bleeds through the packing or fails to improve in spite of adequate blood replacement immediate laparotomy and hysterectomy are indicated.

4. The low incidence of traumatic uterine rupture is a marked improvement over previous reports and is highly commendable. Although of low incidence the condition has a disastrous mortality. This can be reduced, if, after any operative vaginal delivery, particularly version and breech extraction, breech extraction and midforceps, the lower uterine segment is carefully explored, the injury recognized, the uterus packed, and blood administered continuously until the operating room can be made ready for the performance of a hysterectomy.

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A METHOD OF ISOMETRIC PELVIMETRY WITH ACCURATE OUTLET MEASUREMENTS

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SINCE 1923 when Chassard and Lapine[1] tried to measure the adequacy of the subpubic angle by x-ray, various attempts to obtain an accurate method of determining the capacity of the outlet have been made. While the incidence of outlet contraction is relatively low, the gravity of a contraction at this plane is proportionately great.

In 1947 Moir[2] reported a series of ninety-eight cases in which dystocia was predicted. Twelve of these predictions were erroneous. Moir is to be complimented for such accuracy in prediction, especially when one realizes that eight of the twelve errors were made at the plane of the outlet. This suggests either some unknown factor altering the predictability at that plane, or an inaccurate method of determining the capacity of the outlet. Moir suggests that the error is due to his inability to forecast the amount that the lower pelvis expands during labor. Allen[4] in 1943 ably described in detail many sources of error in various methods of outlet evaluation including a method such as Moir's. In a separate comprehensive report[3] concerning the reliability of various methods of interpretation of x-ray pelvimetry using the Steele and Javert[5] technique, the authors have shown that the measurements ordinarily made by most workers at the outlet are more inaccurate than measurements made at other planes. In addition, it was found, in an attempt to deliver a preserved, stillborn fetus through a dried pelvis with a contracted outlet, that the conventional intertuberous diameter was not involved in obstruction of passage of the head. Nor were the tuberosities found to be a factor in failure of forceps delivery in this situation. It was found, instead, that the head either impinged on the pubic arch and the tip of the sacrum in descent, or it impinged on the tip of the sacrum as the head was extended after the occiput had passed under the arch. In other words, not only is the intertuberous diameter inaccurately measured, but also, it is very rarely the diameter which obstructs labor at the outlet. A new method of outlet evaluation was therefore sought.

Factors Influencing Radiographic Technique

Three films are taken on all patients, namely, an anteroposterior, lateral, and pubic arch. The lateral and anteroposterior films are essentially those of Steele and Javert, except for a slight variation which will be described later. This technique is preferred because it is simple, accurate, and inexpensive. The pubic arch film is taken by having the patient sit with the cassette beneath her and stoop forward as far as possible while the tube is centered over the tuberosities, using a tube-film distance of 36 inches. If, in this pubic arch film, one could get the patient to stoop forward sufficiently to bring the ischiopubic rami parallel to the film in all cases, evaluation of the outlet would be extremely simple. Allen[4] states that each film should be checked to determine the amount

that each particular patient deviated from this ideal position, and in those cases where the deviation was significant, the films should be discarded. The necessity of checking each pubic arch film is illustrated in Fig. 1. Let K represent the distance from a point midway between the tuberosities to the bottom of the symphysis. Line AB represents the table top; θ is the angle which the pubic arch makes with the film. When the tube is centered over the tuberosities X represents the distance from a point midway between the tuberosities to the bottom of the symphysis as it appears on the pubic arch film. X obviously does not equal K, and does vary proportionately with angle θ. Since K can be measured on the lateral film (Fig. 3) and X can be approximately measured on the pubic arch film (Fig. 4) the angle the patient stoops, namely, θ, can be determined by the formula $\text{cosine } \theta = \frac{\text{X (measured on pubic arch film)}}{\text{K (measured on lateral film)}}$ For convenience, a cosine table is included in Table I.

TABLE I.

ANGLE	COSINE	ANGLE	COSINE
5°	.9962	50°	.6428
10°	.9848	55°	.5736
15°	.9659	60°	.5000
20°	.9397	65°	.4226
25°	.9063	70°	.3420
30°	.8660	75°	.2588
35°	.8192	80°	.1736
40°	.7660	85°	.0872
45°	.7071		

It should be noted that K, on the lateral plate, is taken from the lower inner border of the symphysis to that portion of the tuberosities which casts the shadow of the terminal end of the ischiopubic rami when the patient is stooped forward for the pubic arch film. The method used to measure X on the pubic arch film appears at first glance to be inaccurate. It is accomplished by measuring X on a distorted scale; the scale is made by taking a picture of a lead centimeter ruler placed 4 cm. off the table with a tube-film distance of 36 inches.*

This method of determining the amount the patient stoops is simpler and more accurate than the method used by Allen,[4] since he uses the tip of the sacrum on the pubic arch film as one of the "end points." The latter "end point" is very difficult to visualize.

On the lateral film, taken by the Steele and Javert method,[5] the lower portion of the symphysis is almost invariably invisible due to the superimposed shadows of the femurs. The necessity of being able to see that particular portion of the symphysis for outlet evaluation prompted us to devise a method of taking the lateral plate in which the position of the femurs was below the lower border of the symphysis.

The table used by Steele and Javert in taking the lateral film was redesigned by lowering one-half of the length twenty-five degrees. Therefore, when the patient is lying on the table so that the tuberosities are at the junction of the horizontal and lowered portions, the femurs are lowered about twenty-five degrees. This accomplished the following favorable objectives:

1. The femurs no longer obstruct the view of the symphysis on the lateral film.

*The distortion is equivalent to 0.4 cm. per 10 cm. Four cm. was found to be the average distance from the table top to the point midway between the bottom of the symphysis and the tuberosities when the lateral films were taken of the patient in position for the pubic arch film. The distortion is equivalent to 0.1 cm. for every 10 cm. on the ruler, per 1 cm. alteration in the height of the ruler. The inaccuracy of measuring X with this scale is therefore negligible.

2. The patient is able to stoop farther for the pubic arch film, thus increasing the accuracy of the picture.

3. The patient does not have to be moved from one table to another between the taking of the anteroposterior and lateral films. This has the advantage both of increasing the accuracy of the measurements and of saving time for the technician. The newly designed Camp grid cassette[6]* is used in the shelf beneath the special wooden table for the taking of the anteroposterior and the pubic arch films.

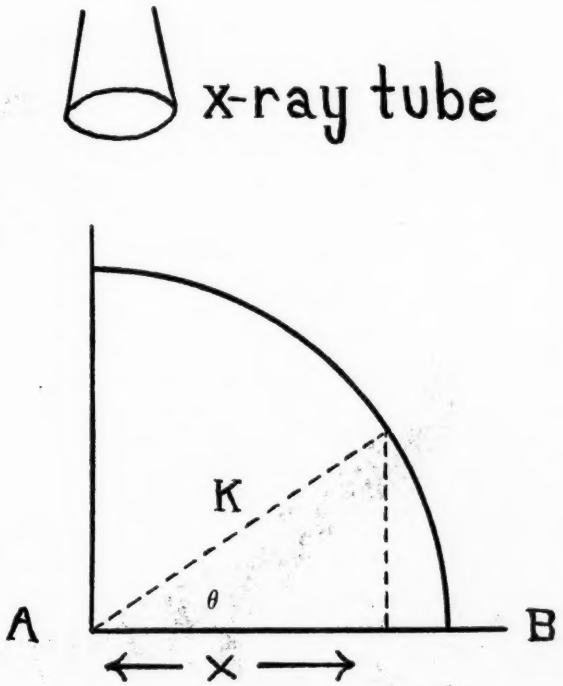

Fig. 1.—Measurement of angle of stoop of patient.

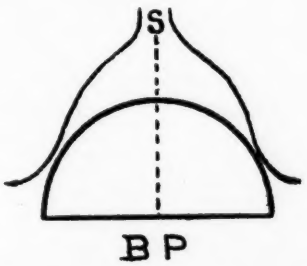

Fig. 2.—Measurement of symphysis-biparietal diameter.

The details of the Steele and Javert[5] technique of taking the anteroposterior and the lateral films have appeared in the American literature at least three times[5, 7, 8] and it seems unnecessary to repeat them at this time. Except for the redesigning of the table as mentioned above, the technique has not been altered. It is imperative that the femurs should be lowered in the anteroposterior as well as the lateral film to avoid a significant error in measurement.

*Sold by Picker X-Ray Corporation.

Measurements Made on the Films

The following measurements are made on these films:

I. Lateral Film.—

1. The obstetrical conjugate (CO) is taken from the upper inner border of the symphysis to the point where the iliopectineal lines meet on the sacrum. The posterior "end point" is varied, however, to get the shortest obtainable CO, as emphasized by Allen.[9] This is necessary, for instance, when the sacrum is convex, or the sacral promontory projects into the inlet.

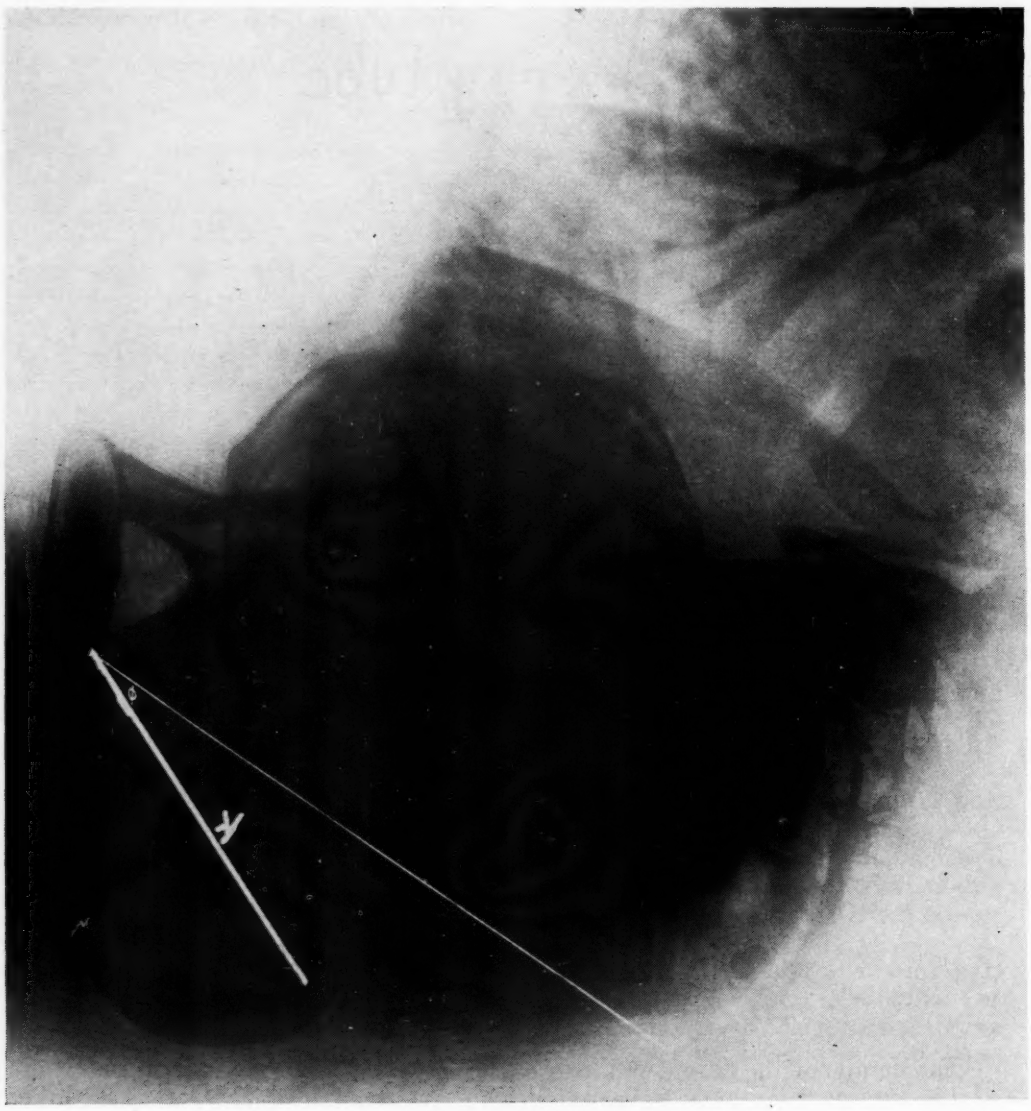

Fig. 3.—Lateral film.

2. The anteroposterior of the midpelvis (APM) is taken from the lower inner border of the symphysis to the junction of the fourth and fifth sacral vertebrae.

3. The posterior sagittal of the midpelvis (PSM) is taken from the junction of the fourth and fifth vertebrae to the point midway between the bases of the spines.

II. Anteroposterior Film.—

(The distortion scale of Steele and Javert is used for making these measurements.)

1. The greatest transverse diameter of the inlet (T) is measured, the "end points" of which are self-explanatory.

2. The anterior transverse diameter of the inlet (AT) is measured from points on the inlet shadow nearest the thinnest portion of the acetabula.

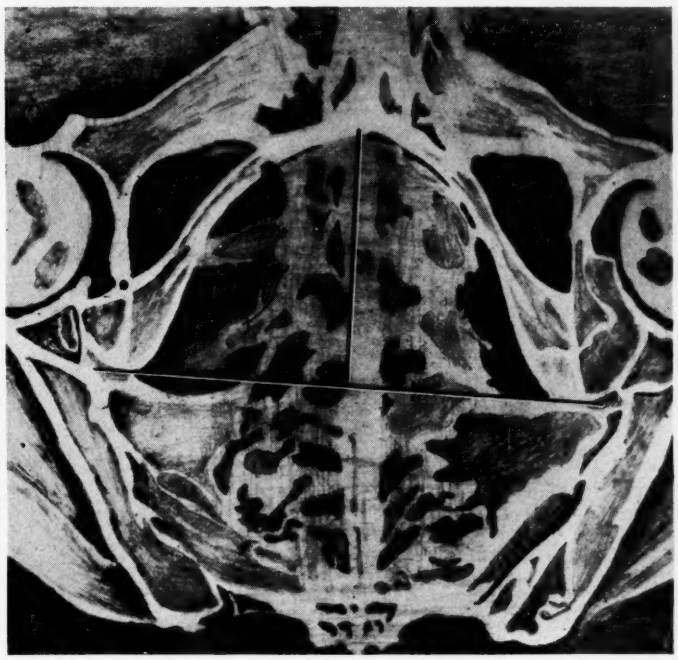

Fig. 4.—Pelvic arch.

3. The true transverse of the midpelvis (TT) (Fig. 3) is measured from points just anterior to the bases of the spines and evaluated on the distortion scale on the same level as the spines are measured. The importance of this measurement was described by Allen.[9] He states: "In other words, . . . 64 per cent of the sagittal diameter lies in front of the bispinous diameter, and only 36 per cent behind it. Furthermore, the spinous processes project into the pelvic cavity from the bodies of the ischia, of which they are, in fact, merely excrescences whose degree of development bears no constant relationship to other features of the obstetrical pelvis. . . . The fetal head, descending in the main posteriorly in the pelvis, will, in the first instance, engage the bispinous diameter in preference to the anterior transverse and if the bispinous is ample, will pass posteriorly. But if, . . . the bispinous is reduced below 100 mm., the skull will pass with its greatest diameter into the more ample space available between the bodies of the ischia. It is clear that something of this sort must occur frequently."

III. The Pubic Arch Film.—

1. This film must first be evaluated to determine if the stooping of the patient was adequate, as has been described.

Fig. 5.—Anteroposterior film.

2. If the film is found to be satisfactory, a semicircle with a diameter of 103 mm. (representing a fetal head distorted proportionately as the pubic arch is distorted) is superimposed on the pubic arch film as shown in Fig. 2. Diameter S-BP is read directly with a nondistorted ruler. This is called the symphysis—biparietal distance by Allen.[4] Calipers are then used to determine that distance on the distorted ruler of the lateral film. One end of the calipers is then placed on the lower inner border of the symphysis on the lateral film and the other end is used to mark an arc of a circle on the film in the region of the spines, the radius of the arc being the S-BP distance. A line is drawn from the lower inner border of the symphysis to the tip of the sacrum. The point where this latter line crosses the arc is used as the anterior end point of the "available posterior sagittal" diameter of the outlet. The posterior end point of this latter diameter is the tip of the sacrum. Obviously, the length of this avail-

able posterior sagittal diameter varies with the amount of space wasted under the symphysis and with the position of the tip of the sacrum. These are the most important factors in obstruction of labor at the outlet.

Interpretation of the Measurements

At the planes of the inlet and midpelvis, the capacities are determined by their respective computed areas. The increased accuracy in prediction of outcome of labor when using these areas has been shown by Allen.[9] A table containing computed areas makes computation at the time of the reading of each film unnecessary. Nicholson[10] states that an inlet area of 90 sq. cm. allows the passage of 70 per cent of heads, and an area of 100 sq. cm. allows 97 per cent of heads to pass. An average head occupies about 70 to 75 sq. cm. The remainder of the space is necessary for soft tissues. A larger area is necessary in breech presentation since molding of the head does not occur.

Morphology is not used for prediction, since a satisfactory quantitative method of classification of pelves has not been devised. A subjective method of evaluating the morphology from these plates is inaccurate, as has been shown in a separate report.[3] We have an insufficient series of cases to present a numerical figure for the measurement of the available posterior sagittal which should be considered contracted. An additional factor which may influence the capacity of the outlet is the angle which the ischiopubic rami make with a line drawn from the lower inner border of the symphysis to the tip of the sacrum (angle ϕ on Fig. 3). If this angle is narrow, it would seem that the head would encounter the pubic arch sooner, thus decreasing the possibility of permitting passage. A large series of cases is necessary to determine the significance of angle ϕ and its relationship to the available posterior sagittal diameter and the relationship of both to the outcome of labor.

Summary

In an effort to obtain greater accuracy in the prediction of the outcome of labor from x-ray pelvimetry a search was made for sources of error in technique and interpretation. It was found that a great percentage of errors in prediction occurred at the plane of the outlet. Another important observation was that the conventional intertuberous diameter was rarely involved in obstruction of labor at that plane. Rather, the head was stopped by either a short diameter between the symphysis and the lower tip of the sacrum, or by the tip of the sacrum as the head was extended under the symphysis. In the latter situation, the capacity of the pubic arch is obviously of utmost importance. If the arch is too narrow, the head is forced toward the power part of the sacrum. A method of evaluating the outlet is presented which has the advantages of taking into consideration the important factors involved in outlet contraction, as well as having definite "end points," which can be clearly seen on the film. In order to visualize the symphysis more clearly on the lateral film, a table was designed on which the patient's legs are lowered, thus preventing the femurs from being superimposed on the symphysis.

This method should be used with a large series of cases to determine how much space is actually necessary at the outlet. In addition, the significance of the angle which the pubic rami make with a line drawn from the lower inner border of the symphysis to the tip of the sacrum should be determined in this proposed series.

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Glaser, Kurt, Parmelee, Arthur H., and Hoffman, William S.: Comparative Efficacy of Vitamin D Preparations in Prophylactic Treatment of Premature Infants, Am. J. Dis. Child. **77**: 1, 1949.

The efficacy of four vitamin D preparations in preventing rickets and allowing normal growth was studied in 166 premature infants for the first eight months of their lives.

The preparations used were (1) vitamin D_2, made by electron bombardment of ergosterol, (2) viosterol, or D_2, made by ultraviolet irradiation of ergosterol, (3) crystalline vitamin D_2 and (4) Delsterol, D_3, made by irradiation of 7-dehydrocholesterol.

The dosages were 100 units, 200 units, 400 units, and 800 units daily. The important observation was that no case of clinical rickets occurred in any of the groups. However, there was roentgenographic evidence of enlargement, cupping, and fraying of the epiphyseal lines and elevation of serum alkaline phosphatase concentrations. Phosphatase levels above 15 Bodansky units per 100 c.c. occurred in twenty-nine instances, of which twenty-three were unaccompanied by any evidence of rickets.

It is believed that 20 units per 100 c.c. represent a better normal upper limit for premature infants.

Gain in weight and length was uniformly good in all 166 infants, regardless of the dosage or the type of vitamin D used.

The authors agree that 100 units of vitamin D are a satisfactory prophylactic dose for most premature infants. However, they suggest that 400 or 800 units daily allow a greater margin of safety in cases of illness or temporary neglect. JAMES P. MARR.

Adams, John M.: Congenital Pneumonitis in Newborn Infants, Am. J. Dis. Child. **75**: 544, 1949.

The author reports six newborn infants with congenital infections of the respiratory tract. A relation between infections of the upper respiratory tract in mothers and primary pneumonitis in their infants is most likely. It is suggested that the same causative agents may be involved and that this agent may be responsible for pathologic changes in the pharyngeal epithelial cells of both the mother and her baby. These changes are represented by large numbers of typical cytoplasmic inclusion bodies seen in the pharyngeal epithelium of both the mother and baby and in the alveolar and bronchial epithelium of the infants who die of pneumonitis.

A brief review of the pertinent features of primary virus pneumonitis is presented, with therapeutic suggestions. Normal human serum U.S.P. and concentrated human gamma globulin appear to be beneficial, particularly when given early in the course of the disease. JAMES P. MARR.

AN EVALUATION OF THE RADICAL HYSTERECTOMY IN THE TREATMENT OF CARCINOMA OF THE CERVIX*

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WINSTON-SALEM, N. C.

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SURGERY was the only available treatment for cancer of the cervix before 1912. The most popular and successful surgical procedure at that time consisted of the removal of all the upper genital structures, the pelvic lymphatic system, and the upper portion of the vagina and was known as the Wertheim operation or radical hysterectomy. With the advent of irradiation treatment, the therapeutic pendulum swung to nonoperative treatment and remained there until recent years. There were three main reasons for this change: (1) 50 per cent of the patients were inoperable; (2) the primary operative mortality varied from 20 to 27 per cent; (3) irradiation therapy offered a much lower primary mortality rate, a universal application, and a satisfactory salvage rate. As late as 1938, one of the leading gynecologists[1] in the United States considered the Wertheim procedure obsolete.

During the past ten years, there has been an increasing interest in the surgical treatment of cancer of the cervix, either alone or in combination with irradiation. The results published to date indicate that surgery has a promising role in the treatment of cervical cancer. The purpose of this paper is to discuss our experience with the Wertheim operation in an effort to improve the present rate of salvage from this disease.

Material

Only service or private patients admitted to the Department of Obstetrics and Gynecology of the Bowman Gray Medical School are included in this study. A larger group of patients with carcinoma of the cervix was admitted to the Department of Surgery or the Department of Radiology. None of the latter patients were subjected to surgery and will, in the future, provide an excellent control series. Twenty-five, or approximately 25 per cent, of the patients admitted to the department of Obstetrics and Gynecology, between the years 1944 and 1948 were subjected to the Wertheim procedure. These twenty-five patients constitute the clinical material for this report.

Observations

General Data.—

The average age of these patients was 40 years, the oldest being 53, and the youngest 28. Four patients had never been pregnant. The remaining 21 had all been pregnant one or more times, with an average parity of 3.1. Twenty-three were married, one was a widow, and one was single.

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

GENERAL DATA

Average age	40.3 years
Oldest	53 years
Youngest	28 years
Nulliparous	4
Multiparous	21
Average parity	3.1
Married	23
Widow	1
Single	1
Private	8
Service	17

Initially five of the service patients were seen as private patients, but were transferred to service because of the financial obligations attached to our method of treatment, which requires x-ray, radium, and a major surgical operation.

There were two outstanding presenting symptoms, abnormal vaginal bleeding and vaginal discharge. Abnormal vaginal bleeding was present in 17 of the 25 patients.

PRESENTING SYMPTOMS

		NUMBER	AVERAGE DURATION OF SYMPTOMS
Abnormal vaginal bleeding		17	11 months
Posttraumatic	6		
Nontraumatic	9		
Postmenopausal	2		
Vaginal discharge		6	13 months
Lower abdominal pain		1	
None		1	

Fifteen of the patients developed abnormal bleeding prior to the menopause; two patients exhibited postmenopausal bleeding. The average duration of abnormal bleeding was eleven months. The duration of this symptom varied from three weeks to three years. Six patients complained of vaginal discharge with an average duration of thirteen months. One complained of pain in the lower abdomen without bleeding or discharge; one had no symptoms, and her case was discovered on routine examination.

With few exceptions, patients admitted to the service of Obstetrics and Gynecology with carcinoma of the cervix in clinical stage I or II were subjected to surgery.

CLINICAL STAGE

STAGE	WERTHEIM
I	15 (preinvasive 2)
II	4
III	5
IV	0
Unknown	1

The remainder received only deep x-ray and radium therapy. In addition, five cases of Stage III were subjected to the radical hysterectomy after irradiation since there was no evidence of disease. With two exceptions, all of the patients were subjected to x-ray and radium therapy prior to surgery. The tabulation of Clinical Stages reveals the incidence of surgical treatment in the various clinical stages of the disease according to the League of Nations classification.

Pathologic Grade.—

It is obvious from the clinical and pathologic classifications that in the patients who received surgery early lesions predominated.

PATHOLOGIC GRADE

GRADE	NUMBER OF CASES
I	7 (Preinvasive 2)
II	8
III	8
IV	1
Unknown	1

All of the tumors were graded pathologically. Seven were Grade I, two of which were preinvasive. Eight were Grade II, eight Grade III, one Grade IV, and in one case the Grade was unknown as the pathology was done elsewhere.

Preoperative Irradiation.—

Nearly all of the patients received a total of 8,120 r. of deep x-ray therapy and 4,000 to 6,000 mg. hr. of radium.

Surgery.—

With the exception of a few patients with preinvasive and very early invasive carcinoma, a complete radical hysterectomy, according to the Wertheim technique, was done. The patients who were not subjected to the complete Wertheim operation, had a so-called modified procedure. This included all of the dissection except that of removal of the iliac and aortic lymph nodes. Metastatic lesions were encountered on two occasions. A positive node was found at the bifurcation of the aorta once, and a 3 cm. mass of carcinoma in the left broad ligament in another case.

Spinal Pontocaine was used in twenty-two of the operations, cyclopropane and ether in two, and spinal Nupercaine in one. Pentothal, Sodium gas, and ether were used to supplement the initial spinal anesthetic in all but ten cases. One of two members of the senior staff either performed or assisted in every operation. The average operating time was two hours and thirty-five minutes. The longest operation required four hours and twenty minutes, and the shortest one hour and fifty minutes.

No effort was made to prevent the occurrence of shock by the prophylactic use of fluids or blood. Blood, plasma, and fluids were given only when indicated by the patient's condition. Ten patients received one transfusion during the operation, but in no case was the shock alarming. The maximum drop in systolic blood pressure was 20 points. Fifteen patients received fluids and/or blood during the procedure for the same reason. Ten patients showed no evidence of shock, and, therefore, received no fluids during the operation. Postoperatively, twenty-four of the patients showed no reaction. One patient developed a mild fall in blood pressure which was corrected by the administration of intravenous fluids.

Postoperative Complications.—

There were a large number of postoperative complications, 16 of which were due to urinary tract infection. The majority of the latter were relatively harmless and attended by a short clinical course with little or no disturbance to the patient. However, several were severe and strongly suggested primary injury of the urinary tract precipitating the infection. In addition, there were 3 cases of pelvic cellulitis, 1 of peritonitis, 1 of evisceration, 1 pelvic abscess, 1 pulmonary embolism, 1 ureteral obstruction, 1 hydronephrosis, 2 rectovaginal fistulas, 1 vesicovaginal fistula, and 1 death. Some of these complications were overlapping and therefore do not represent a total rate of morbidity.

POSTOPERATIVE COMPLICATIONS

COMPLICATIONS	NUMBER
Urinary tract infection	16
Pelvic cellulitis	3
Rectovaginal fistula	2
Vesicovaginal fistula	1
Pelvic abscess	1
Wound disruption	1
Peritonitis	1
Pulmonary embolism	1
Ureteral obstruction	1
Hydronephrosis	1
Death	1

We would like to discuss briefly five of these cases since they constituted the major portion of our complications.

Case Reports

CASE 1.—Mrs. G. J. D., NCBH No. 57501. A diagnosis of Stage I, Grade II squamous-cell carcinoma of the cervical stump was made in the Out-Patient Department. The patient received 8,120 r. of deep x-ray therapy and 4,200 mg. hr. of radium. Six weeks after the radium, a Wertheim operation was done. During the operation, the bladder was accidentally opened and repaired immediately. Postoperatively, she had considerable fever with a rapid pulse rate and clinical evidence of peritonitis. Repeated urinalyses showed numerous white cells and a culture of the urine revealed a pure growth of *Escherichia coli*. She subsequently died on the nineteenth postoperative day in spite of massive chemotherapy, blood transfusions, and other supportive measures. Autopsy revealed a vesicovaginal fistula, a rectovaginal fistula, and an ascending retroperitoneal cellulitis on the left side, with atelectasis of the left lower lobe of the lung.

CASE 2.—Mrs. N. H. W., NCBH No. 28988. A diagnosis of Stage I, Grade I squamous-cell carcinoma of the cervix was made in the Out-Patient Department. Six weeks after the completion of irradiation therapy, she had a Wertheim operation. During her operation the right ureter was sectioned inadvertently. It was transplanted into the bladder. She ran a very prolonged febrile postoperative course and received large quantities of intravenous fluids, blood, and various chemotherapeutic agents. Postoperatively she developed an acute urinary tract infection from which was cultured *Escherichia coli*. She developed a pelvic cellulitis. On the twenty-first day she had a pulmonary embolism. She gradually recovered from this and was discharged fifty-one days postoperatively. Since her discharge, she has been seen in the Out-Patient Department and is perfectly well without recurrence and without evidence of permanent renal damage.

CASE 3.—Mrs. R. G. A., NCBH No. 74619. A diagnosis of Stage II, Grade I carcinoma of the cervix was made in the Out-Patient Department. The patient received 9,474 r. of deep x-ray therapy, followed by 1,800 mg. hr. of radium. The radium was removed before the full dosage because of a temperature elevation of 102° F. Four months after the radium therapy, she was admitted to the hospital and a Wertheim operation was performed. Postoperatively the temperature rose abruptly to 104° F. and stayed at that level for many days thereafter. Repeated urinalyses revealed a severe urinary tract infection due to *E. coli*. Urinary tract studies revealed a bilateral hydronephrosis with nephroptosis, a finding which had not been noted on previous urologic studies. Her clinical picture indicated the presence of peritonitis. She was allowed out of bed on the twenty-eighth day and was discharged on the fiftieth day. She was seen two months after her discharge, at which time she had no symptoms. Urinalyses, however, revealed a chronic pyelonephritis and further studies showed a persistent hydronephrosis on the left. It was our opinion that there was an operative injury of the urinary tract, resulting in a chronic and persistent urinary infection.

CASE 4.—Mrs. A. C. S., NCBH No. 24232. This patient had a Stage III, Grade II squamous-cell carcinoma of the cervix. She received an initial dose of 4,050 mg. hr. of radium which was followed by 3,744 r. of deep x-ray therapy. Six months later she had a Wertheim operation which was uneventful. Postoperatively there was moderate abdominal distention, anorexia, nausea and vomiting which required a total administration of 6,000 c.c. of fluids over a period of five days. She also received chemotherapy postoperatively for approximately one week. On the ninth day she suddenly disrupted her incision. An immediate repair was done and healing was complete in seven days. She was allowed out of bed on her first postoperative day and was discharged on the twenty-fifth postoperative day. She was last seen 3 years after her initial visit at which time she was asymptomatic and there was no evidence of recurrence.

CASE 5.—Mrs. G. B. NCBH No. 40756. This patient was found to have a Stage I, Grade I squamous-cell carcinoma of the cervix. Six weeks after irradiation a Wertheim operation was done without complications. During the operation she received no fluids but postoperatively she required supplemental fluids by vein for several days. She was allowed out of bed on the fourth postoperative day and was discharged on the eight postoperative day. When she returned for her first follow-up examination, she was found to have a rectovaginal fistula which has persisted until the present time. It now measures 2 mm. in diameter but fecal material is rarely passed per vaginam. She has been on Sulfathalidine for two years. Our present plan of therapy is to repair the fistula after she has been free of any evidence of malignancy for a period of five years.

One of the best indices of operative morbidity is the length of time the patient remains in bed, and/or in the hospital. The duration of hospitalization, in our experience, depends upon the distance the patient lives from the hospital. Therefore, the time required for the patient to become ambulatory seems to be of more significance in establishing the immediate postoperative morbidity. The average hospital stay was found to be sixteen and one-half days for the entire group of patients. The longest was fifty-one and the shortest seven days.

AMBULATION AND DISCHARGE

DAYS	UP	DISCHARGED
1-5	19	0
5-10	2	7
10-15	1	9
15-20	0	3
20-25	0	3
25-30	1	0
35-40	0	0
40-45	1	0
45-50	0	2

The average time required for ambulation was seven days. However, eliminating three patients who were confined to bed for 19, 28, and 42 days, respectively, the average duration of complete bed rest would be only four. The patients were gotten up as soon as possible after their operation. Some febrile patients were allowed out of bed when the cause of the fever was found to be a urinary tract infection. It can be seen from this that the majority of the postoperative complications were not serious enough to render the patient unable or unwilling to get out of bed.

Follow-Up.—

Twenty-two patients have been seen for follow-up examination, two have just recently been operated upon, and the other patient died. The longest follow-up period is three years and in no case has active cancer been noted. Seventeen of the patients were asymptomatic and free of any evidence of recurrence. Two patients had metastatic lesions at the time of surgery. One

patient had a mass 3 cm. in diameter in the broad ligament which appeared following irradiation and did not appear to be a lymph node, and the other patient had a positive node at the bifurcation of the aorta. In neither case was there any evidence of recurrence; however, both cases have been followed less than two years. Pelvic induration was noted in three of the patients, the significance of which will have to be evaluated at a later date, since all three are relatively recent cases. Two patients had chronic urinary tract infection which has required repeated urologic treatment, and one patient has a recto-vaginal fistula.

We have presented a brief summary of the preceding twenty-five cases for the purpose of showing our experience with the radical hysterectomy in the treatment of carcinoma of the cervix. No one, as yet, has reported sufficient material, or has had sufficient follow-up to compare their long-range results with those of patients treated with radiation alone.

Discussion

Although irradiation therapy for cancer of the cervix is relatively satisfactory, particularly in the early cases, the results are still far from desirable. This, plus the encouraging preliminary reports in regard to the Wertheim procedure, led us, in 1944, to carry out the radical Wertheim pelvic operation on certain select cases for several reasons. The first is that the majority of patients dying of cancer of the cervix die from a pelvic recurrence and the complications associated with it. Behney,[2] reported 166 autopsies done on patients with terminal carcinoma of the cervix. Ninety-six of the deaths in this series were attributed to complications of the malignancy. Approximately 50 per cent of the autopsies revealed that the cause of death was secondary to pelvic recurrence of the cancer. Brunschwig and Pierce,[3] in 65 autopsies on patients with cancer of the cervix, found that 66 per cent of the patients died from uremia or sepsis. Death from distant metastases is rare. The usual cause of death from cervical cancer is pelvic recurrence and its sequelae. Ureteral obstruction with uremia, infection and erosion of large vessels with hemorrhage are common. It would, therefore, seem that an extirpation of the tissues in which the tumor recurs should improve the results of treatment.

We have done repeated biopsies on patients after treatment for carcinoma of the cervix. In spite of complete x-ray and radium therapy, active malignant cells were found in a large number of patients many months after treatment had been completed. Meigs[4] has noted persistent lymph-node involvement following presumably adequate x-ray therapy. He states that he prefers surgery to irradiation in any operable case.

The mortality, associated with any type of treatment is of utmost importance in its evaluation. The primary mortality of the Wertheim operation, when it was initially introduced, was appalling. According to Read,[5] Bonney, who for years has used the operation for all operable carcinomas of the cervix, has an over-all mortality of 14 per cent. This has been reduced in the latter part of his series to 11 per cent. More recent reports,[4, 6, 7, 8] indicate a much lower mortality rate, probably due to the fact that these cases have been more carefully selected. Most of the figures now approximate 5 per cent of the primary operative mortality. Whereas the mortality rate associated with surgery will

probably always remain greater than that with irradiation, the increased number of lives salvaged by surgery should more than offset this. Furthermore, the operative mortality will gradually be reduced as we gain more experience with the procedure.

At the present time there is universal agreement that Stage I, Stage II, radioresistant Stage III, and adenocarcinoma are considered suitable for surgery. At the present time we feel that all patients should receive the benefit of the well-established salvage offered by irradiation therapy. With an attempt to improve the anticipated salvage rate by performing a Wertheim operation after full irradiation therapy, five patients with Stage III carcinoma of the cervix were found to be free of any evidence of cancer and were, therefore, subjected to surgery.

The frequency of urinary tract complications was expected since the ureters and bladders are dissected extensively. We hope, with increased experience, to be able to reduce the frequency of trauma and infection to these structures. Whether or not the Wertheim operation will improve our present salvage rate remains to be proved. At the present time no one has had a sufficient number of operations or an adequate period of time to evaluate properly the results of treatment with surgery.

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Discussion

DR. C. J. ANDREWS, Norfolk, Va.—Evaluation of the place of radical pelvic surgery in the treatment of carcinoma of the cervix must await the accumulation of accurate five-year survival rates from recent studies, such as that just reported, conducted after the advent of chemotherapy and blood banks. These must be compared with cases currently treated with irradiation only.

Regardless of the eventual fate of these twenty-five patients, Drs. Donnelly and Caldwell are to be congratulated on the excellent technical results achieved in this group, which again demonstrates the practicability of the surgical approach. The primary operative mortality of 4 per cent is quite low compared to the earlier results by the most expert surgeons such as Victor Bonney, with 14 per cent. This apparently can be made even lower in larger series with careful selection, such as current ones by Meigs and Brunschwig. The sole mortality in *this* series occurred in a case of cacinoma of the cervical stump, a predictably more difficult case. The operative mortality thus approaches that from irradiation alone.

The risk of urinary fistulas resulting from operation and from irradiation, in general about 7 per cent each for all stages, might be expected to be at least partly additive where both procedures are used in the same patient. So far, in this series of early cases, the incidence of 4 per cent is quite low. Later damage from irradiation may yet be encountered.

Since there is such a wide variation in the interpretations of the term "Wertheim operation" it would seem desirable for the authors to specify the exact procedure used in their cases. As recently emphasized by Brunschwig, the operation as done by Wertheim included

little or no dissection of the pelvic glands. The authors imply that *aortic* lymph nodes are removed in most of their operations. This would seem to be a most unusual procedure and possibly represents a difference in terminology that needs to be clarified.

In regard to preinvasive or intraepithelial carcinoma, I believe the diagnosis should be made with great care, only after examination of repeated biopsies by one thoroughly familiar with gynecological pathology. It should be ascertained that the patient is not pregnant and has not recently been pregnant, for changes indistinguishable from intraepithelail carcinoma, which later disappear, may be observed in pregnancy. The work of Galvin and Te Linde is cited as evidence of the invasiveness of intraepithelial carcinoma. They have not done a gland resection with their operations and have no recurrences over a significant number of years. Their operation includes resection of a parametrial and vaginal cuff. Gland resection in the definite cases of intraepithelial carcinoma would seem an unnecessary additional hazard.

Information concerning the incidence and location of viable carcinoma in the specimens removed in the twenty-five cases just reported and in future cases so treated would be an interesting addition to the knowledge of the effects of irradiation therapy.

It should be emphasized that this operation requires the highest surgical skill and experience and should, I believe, be limited at present to carefully regulated investigation.

Phaneuf, Louis E., and Graves, Roger C.: Vesicovaginal Fistula and Its Management. With a Description of an Intravesical Operation for Certain Difficult Cases, Surg., Gynec. & Obst. **88**: 155, 1949.

The authors present a brief historical discussion of the first successful closure of vesicovaginal fistula. They point out that contrary to current belief Mr. Montague Gosset performed the first operation using gilded silver wire in 1834. They discuss also the work of J. Marion Sims and his use of silver wire. The various operative procedures used in closing vesicovaginal fistula are tabulated. Although the authors feel that most of these can be closed by the vaginal approach, a few cases necessitate the abdominal route, and some require ureterointestinal anastomosis. The technique for abdominal closure of vesicovaginal fistula is described in detail with illustrations. Six cases of ureterointestinal anastomosis are also described. The pre- and postoperative care of these patients is given in some detail.

L. M. HELLMAN.

Lukins, J. B., and Lukins, Lanier: Hysterectomy, South. M. J. p. 132, Feb., 1949.

An excellent review of the historical evolution of the hysterectomy operation is presented.

The operation was discussed, but apparently not executed before the Christian era.

The vaginal hysterectomy was first performed about A.D. 1500. Howard Kelly in 1888 brought the hysterectomy technique to a high point of development and reported a mortality of only 5 per cent.

The relative merit of subtotal and total hysterectomy is discussed. The age of the patient, the condition of the cervix, the pathology in the uterus, and obesity all enter into the discussion as to whether or not the cervix should be removed. The author feels that the incidence of carcinoma in the cervical stump must be less than .05 per cent. In women under forty he prefers a subtotal operation, although panhysterectomy may be employed in the younger group when the indication justifies this more radical operation.

WILLIAM BICKERS.

RETAINED PLACENTA: DELIVERY BY THE HYDRAULIC METHOD (MOJON-GABASTOU INJECTION)

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RETAINED placenta is a disagreeable and frustrating complication. It may unexpectedly prevent the termination of normal labor or it may be the final straw of exasperation in a highly pathologic labor. Treatment may range from prompt manual removal to an expectant policy of hands off. In the latter event, the patient is put to bed until the placenta is expelled naturally, which may be in some hours or days. The obvious dangers of such expectancy are hemorrhage and infection. On the other hand, manual removal of the placenta was formerly dreaded because of its alleged mortality of 10 per cent.[1, 2] Obstetricians would avoid or defer it whenever possible, sometimes until the patient's condition had greatly deteriorated. However, this 10 per cent mortality rate has been reduced in recent years to a figure ranging from 1.8 to 2.8 per cent.[3-7] This striking reduction in mortality of manual removal of the placenta has probably been due to three factors: (1) the ready availability of blood since the establishment of blood banks; (2) the existence of effective drugs for combating infection such as the sulfonamides and penicillin; and (3) an increased tendency to perform manual removal while the patient is still in good condition. So much better are the present-day results that some writers have recently swung to the opposite extreme of regarding manual removal as a "benign procedure."[8]

Nevertheless, deaths following manual removal of the placenta are still being reported. A recent casual reading of the literature revealed mention of a death in each of two prominent teaching institutions.[9, 10] In one case the uterus was ruptured during manual removal, hysterectomy was done, following which the patient died.[9] Inversion of the uterus during manual removal has also been reported.[4, 7] Jarcho[11] says instances are known where "an attempt at manual removal has resulted in boring a hole through the fundus and bringing down a loop of intestine through the rent." It follows then that manual removal of the placenta can hardly be considered a simple, innocuous procedure. For this reason, the physician who encounters retained placenta in the small hospital or the home is often reluctant to undertake manual removal. This is especially so in the case of the isolated country doctor who, after failing to deliver the placenta by the Credé method, loads the patient into an ambulance and sends her to the nearest medical center.

The Hydraulic Method

There is, however, a safe, simple method of delivering the retained placenta without invading the uterus by the hand. This procedure, which can be used by specialist and general practitioner alike, is known as the hydraulic method.

When 500 c.c. of hot sterile normal saline solution is injected into the cord through the umbilical vein, expulsion of the placenta from the uterus will occur in a matter of some minutes. The injection of the hot solution causes the placenta to get larger (about twice normal size), firmer, and heavier. The increase in size of the placenta completes its separation from the uterine wall if still attached, while the increased size and weight stimulate uterine contractions. The heat of the injected solution further stimulates uterine contraction.* The patient complains of cramping pain in the abdomen, the uterus becomes very hard, the fundus rises, and frequently a gush of mingled saline and blood appears at the vulva. Following this, the placenta is either expelled spontaneously from the vulva or can be expressed manually.

The success rate of the hydraulic method has been found to be from 70 to 90 per cent in various series of cases ranging in number from 13 to 313.[2, 4, 11-23] Currie[12] who used the hydraulic method in 186 cases of retained placenta reported that the number of manual removals in his clinic fell from twenty-five per year to one or two. The hydraulic method is often called the Mojon Gabastou injection after Juan A. Gabastou[23] of Buenos Aires who discovered it in 1914 and Benedetto Mojon of Genoa, Italy, who anticipated him in the preaseptic era.[11, 15] Gabastou's own designation for the procedure was merely the "hydraulic method." (In the earlier European articles Gabastou's name was erroneously spelled "Gabaston" through a mistake in translating his article from Spanish into German.[24])

Technique

The only equipment needed for the hydraulic method is (1) a large-gauge needle with short bevel or blunt end, (2) a large syringe, (3) several hemostatic forceps, and (4) 1,000 c.c. of hot sterile normal saline solution. These articles are usually at hand or can be readily assembled even in rural areas. If need be the hot sterile normal saline solution can be prepared in any kitchen by adding one rounded teaspoonful of table salt to one quart of tap water which is boiled for ten minutes. The needle is inserted into the umbilical vein of the cord as for any intravenous injection and then clamped with one or two hemostats to maintain it in place and to prevent escape of the fluid from the cord around the needle (Fig. 1). Five hundred cubic centimeters of hot sterile normal saline solution are briskly injected. While the syringe is being refilled the cord must be compressed between the finger and thumb of an assistant to prevent the fluid from escaping back through the needle. When injection is complete another hemostat must be clamped on the cord between the point of injection and the vulva to retain the fluid in the placental circulation. If at the end of fifteen or twenty minutes the placenta has not been delivered either spontaneously or by simple pressure on the fundus, the manual removal should be done without further delay.

The cord should always be injected far enough away from the vulva so that there will be a sufficient length to permit a second insertion of the needle. This precaution is useful not only in case a second injection is required but also where the first injection has failed because of transfixion of the vein by the needle. The needle should have a short bevel or a dull end because its point is less likely to transfix the vein. A 50 c.c. syringe is desirable although a 20 or 30 c.c. syringe may be used. Do not repeat the injection of the placenta when the fluid runs out the vulva as fast as it is injected. This is likely to occur when the placenta has been ruptured by vigorous attempts to express it by the Credé

*Retention of the placenta may be due to incomplete separation from the uterine wall (adherent placenta); inertia of the uterus in the third stage of labor; or a localized spasm or contraction ring in the uterine wall.[12] Placenta accreta is an extremely rare cause of retained placenta and therefore does not come within the scope of this paper. In 15,000 deliveries at Bellevue Hospital, placenta accreta was not once diagnosed.[6]

method. It is therefore incapable of holding the injection fluid which escapes through the broken cotyledons. Further injection is useless and even dangerous, for, if excessive bleeding happens to set in, its magnitude may be masked by the outpouring of normal saline solution.[25] The sterile normal saline solution must be hot when injected, not cold or lukewarm. McIntyre[18] recommends a temperature of 125° F. (52.5° C.).

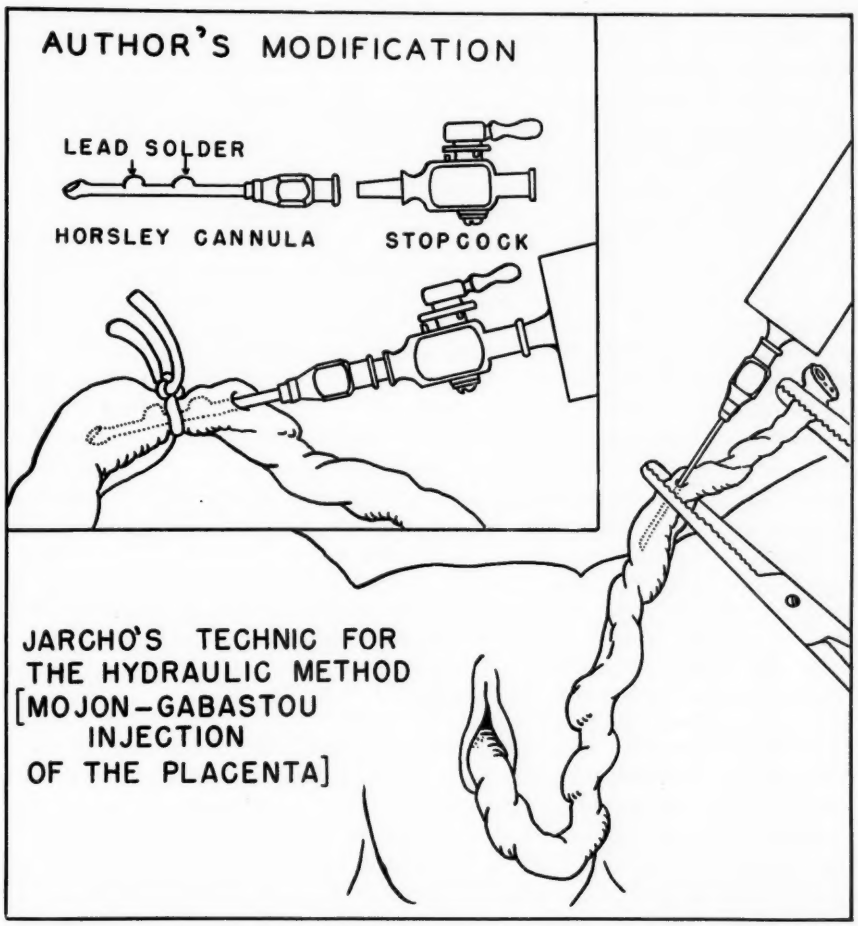

Fig. 1.—Jarcho's simplified technique for the hydraulic method (Mojon-Gabastou injection); a large-gauge, short-beveled, intravenous needle; a 50 c.c. syringe; several hemostats; and hot sterile normal saline solution. While the syringe is being refilled the cord must be compressed by an assistant to prevent backflow. The inset shows the author's modification which makes for greater ease of injection and requires no assistant.

For institutions which do a large amount of obstetrical work the author suggests the refinement shown in the inset of Fig. 1, viz., a Horsley intravenous cannula with two lead knobs soldered on its shaft plus a stopcock which is inserted between the syringe and the Horsley cannula. The lead knobs on the cannula permit it to be tied securely into the umbilical vein and the stopcock prevents backflow while the syringe is being refilled. When the injection is completed the cannula and stopcock are left in place in case a second injection should be necessary. The large bore of the Horsley cannula (No. 13) permits easy and rapid injection and its blunt, rounded end will not transfix the vein as so often happens with the standard needles. The umbilical vein must be opened with scissors to insert the cannula.

Evaluation of the Hydraulic Method

A careful search of the literature has not revealed any dangers inherent in the proper application of the hydraulic method. There is no danger of infection because a sterile fluid is injected by a sterile technique. Tuma,[25] Koerting,[15] and Borberg[2] state that there is no danger of air embolism. Should any of the normal saline solution enter the maternal circulation through the uterine sinuses, the effect is merely that of an intravenous infusion. The hydraulic method is simple. It is safe. It is successful in delivering 70 to 90 per cent of retained placentas. No anesthetic is required. If the injection fails to cause expulsion of the placenta the case is in no way further complicated. One may immediately proceed to manual removal which may actually be made easier because of the increased thickness and firmness of the placenta.

When retained placenta occurs in a case of eclampsia the hydraulic method is far preferable to manual removal because the eclamptic patient withstands shock and general anesthesia poorly. The hydraulic method is especially indicated in the presence of intrapartum infection (as in prolonged premature rupture of the membranes), for it will not stir up and spread the intrauterine infective process as will manual removal. Sisco and Agüero[22] reported that in sixty cases treated by the hydraulic method there were no deaths and a puerperal sepsis rate of only 2.27 per cent. On the other hand, in 282 cases of manual removal there was a puerperal infection rate of 43 per cent with a "corrected" death rate of 1.77 per cent and an uncorrected death rate of 6.12 per cent.

The hydraulic method is not a temporizing measure. It should be used early in order to insure its success, for it is not likely to succeed where the placenta has been retained many hours or several days. In such cases the presence of blood clots in the placental vessels may obstruct the passage of the injection fluid. The hydraulic method is apt to fail when it has been preceded by repeated and vigorous attempts at Credé expression of the placenta. The placenta may be so torn by forceful Credé manipulations that it cannot be distended by the injection fluid, which runs out as fast as injected. Furthermore, the uterine musculature may be so injured that the uterus fails to react with adequate contractions after the placenta has been distended by the normal saline solution. Therefore, the Credé maneuver is best dispensed with entirely not only because it decreases the chance for success of the hydraulic method, but also because of its admitted dangers. Currie[12] has seen serious shock, inversion of the uterus, and rupture of the uterus following the Credé maneuver.

The proper indications for the hydraulic method are (1) retained placenta without bleeding and (2) retained placenta with only slight bleeding. *It is not to be used where profuse bleeding is associated with retention of the placenta. Here, immediate manual removal should be done because it is speedier and more certain.* The hydraulic method is not to be used on a patient who is in shock from blood loss.

Case Reports

The author has used the hydraulic method in thirteen cases of retained placenta with success in nine, or 69.2 per cent. All but two of these placentas had been retained in the uterus over one hour after the delivery of the baby. In the nine successful cases one injection was sufficient in all but one which required a second injection. The intervals between injection and expulsion were as follows: at once, "soon," 5, 6, 20, 12, 4, 5, and 15 minutes. Fundal pressure was used to extrude the placenta from the vagina in eight cases while in one case the placenta was spontaneously expelled from the vagina. The hydraulic method failed in four cases; manual removal was then done without difficulty. The puerperium was normal in all except two cases which had mild to moderate

temperature elevations following blood transfusion. These were the only two cases in the series requiring transfusion. Penicillin was used prophylactically in one case only (a referred case) and the sulfonamides not at all. In no case was the hospital stay prolonged beyond the usual time. For lack of space and to avoid repetitiousness, only four cases will be cited from the author's series of thirteen.

CASE 3.—Mrs. A. W., aged 23 years, primipara at term, twenty-seven hours' labor, mid-forceps delivery. Retained placenta. Treated by the hydraulic method. Placenta expressed from vagina in five minutes. Period of retention, one hour, twelve minutes. Puerperium normal.

CASE 5.—Mrs. A. J., aged 25 years, multipara at term, labor six hours, persistent occiput posterior, Kielland forceps rotation followed by low forceps delivery. Retained placenta. This time cold normal saline solution was injected. The uterus rose high in the abdomen but remained inert. A second injection was done with hot normal saline solution. The uterus soon began to contract and in six minutes the placenta was spontaneously expelled at the vulva. Period of retention, one hour, forty-six minutes. Puerperium normal.

CASE 6.—Mrs. B. D., aged 28 years, multipara at term, labor two hours, low forceps delivery. Retained placenta with slow bleeding. Treated by the hydraulic method. Twenty minutes later placenta easily expressed. Period of retention, one hour, nineteen minutes. Puerperium normal.

CASE 12.—Mrs. T. R., aged 24 years, multipara, thirty-six weeks' twin pregnancy, labor six and one-half hours. Retained placenta with slow bleeding. Each umbilical cord was injected with 500 c.c. hot sterile normal saline solution. Some hard uterine contractions occurred, but the placentas could not be delivered. While repeated attempts at expression were being made, profuse bleeding set in. Without further delay manual removal under ether anesthesia was done. The lowermost placenta was found hanging free in the uterine cavity while the uppermost placenta was still adherent at its superior edge. Period of retention, one hour, fifty-one minutes.

Comments

Case 5 illustrates the importance of using hot normal saline solution for injection. The solution should not be cold nor should it be merely warm. It should be hot. McIntyre[18] points out that if the solution is only at body heat it will cool off as it traverses the cord and by the time it has circulated through the entire placenta it will be much below blood heat. The reason for failure in Case 12 is obvious. In two other failures in the series there were errors of technique. In one the volume of fluid injected was too small (150 c.c.), but a second injection could not be made because the cord had been cut too short. In the other case vigorous expression of the placenta was attempted immediately after injection with the result that the cotyledons burst and allowed the fluid to escape. No reason for failure was apparent in the fourth failed case. Those interested in using the hydraulic method are advised to inject several freshly delivered placentas to gain familiarity with the technique.

In the first two cases in this series of thirteen, the placenta was retained thirty-six and twenty-eight minutes, respectively. In the remaining eleven, one hour or more was allowed to elapse before injection of the placenta with hot sterile normal saline solution. In this way, the author attempted to eliminate cases where the placenta might have delivered in a little more time without being injected.

Summary

1. Retained placenta is a disagreeable, frustrating, and dangerous complication which requires prompt solution.

2. Manual removal of the placenta is not an innocuous procedure to be undertaken lightly in all circumstances. While its mortality has been greatly improved in recent years, manual removal still carries the dangers of rupture of the uterus, inversion of the uterus, shock, hemorrhage, and infection.

3. The hydraulic method (Mojon-Gabastou injection) is recommended as a safe, simple substitute for manual removal, which makes it possible to deliver the retained placenta without invading the uterine cavity with the hand. The placenta is briskly injected through the umbilical cord vein with 500 c.c. of hot sterile normal saline solution, which stimulates the uterine expulsive mechanism.

4. The hydraulic method has been found successful in 70 to 90 per cent of retained placentas in large series of cases reported by various authors. Its occasional failure does not further complicate the case or interfere with manual removal. In fact, manual removal is made easier due to the increased firmness and thickness of the placenta.

5. The hydraulic method should be used *early,* not after many hours or several days of retention of the placenta. In such cases the chance of success is slight due to clotting of the blood in the placental blood vessels.

6. The hydraulic method is indicated in (a) retained placenta with no bleeding and (b) retained placenta with only slight bleeding. It must not be used where retained placenta is associated with profuse bleeding or shock due to previous blood loss. Immediate manual removal is the only rational means of treating profuse bleeding caused by retained placenta.

7. The Credé method, with or without anesthesia, is not recommended for the treatment of retained placenta. It is traumatic, shocking, and too often it is unsuccessful. Should waiting and simple expression fail, the hydraulic method should be used. If the hydraulic method fails, manual removal of the placenta is the next step.

8. The hydraulic method is the treatment of choice for retained placenta in the presence of eclampsia because the eclamptic patient withstands general anesthesia and shock poorly.

9. The hydraulic method is the treatment of choice for retained placenta in the presence of prolonged rupture of the membranes and intrauterine infection because it does not stir up the infective process as does manual removal of the placenta.

10. The hydraulic method is useful not only in the hospital delivery room but should be very useful in rural areas.

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There are reported six deaths, from 1944 to 1946, of patients with toxemia of pregnancy; five of these deaths occurred in one year, in fact, in nine months of this one year. A study of these cases showed that pulmonary edema was either the cause of, or an important factor in, all these deaths, and that the pulmonary edema resulted from excessive administration of fluids. In 1946 and 1947, the method of treating eclampsia has been revised. Sedation with morphine sulfate and chloral hydrate is still employed. Only enough fluid is given daily to replace the insensible loss, calculated as 1,500 c.c., plus the amount of the urinary output in the previous twenty-four hours. Hypertonic solutions are not employed but 5 per cent of glucose is the standard material for use in these cases. This same plan of fluid administration is used in pre-eclampsia as well as eclampsia. In the eclamptic cases ¼ grain of morphine is given intravenously and ¼ grain subcutaneously on admission to the hospital or after the first convulsion; additional morphine is given with thirty minutes between treatments, to reduce the respiratory rate below 14, but not below 10. An enema of 20 to 30 grains of chloral hydrate in 200 c.c. of water may be substituted for the morphine occasionally to avoid excessive morphinization. External stimulation by noises, bright light, needle pricks, and catheterization is avoided. Fluid is administered as described. After the convulsions are controlled, phenobarbital (3 grains daily) is used for sedation. Labor is not induced until at least two days, and preferably three days, after the last convulsion.

This method has been employed in twenty-one consecutive cases of eclampsia (including eight with severe eclampsia according to Eden's criteria) without a maternal death. There were six infant deaths, including two macerated stillbirths; all but one of the other infants were premature; in the case of the one mature infant the cause of death, within a few minutes after birth, was not known and may have been related to labor. The amount of morphine given in this case was relatively small as compared with that used in other cases in which the infants survived. Harvey B. Matthews.

SERUM PHOSPHATASE RELATIONS IN MOTHER AND FETUS

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PROFOUND alterations in the body's economy of calcium and phosphate occur during pregnancy and lactation, to provide for the fetal needs for these substances and for their excretion by the mammary glands. Studies in placental permeability employing tracer doses of radioactive phosphorus have shown, for example, that the guinea pig fetus near term retains in each hour as much phosphorus as the total quantity of this element in the circulating plasma of its mother.[27] Changes in inorganic phosphate as well as calcium in the serum of the pregnant woman are so slight, however, that they are practically completely lacking in significance for the interpretation of metabolic phenomena. Maternal stores are obviously essential to the growth of the fetus. These stores of phosphorus exist in the form of organic esters, the phosphate ions being liberated as needed through the mediation of enzymes, notably alkaline phosphatase.

This enzyme, widely distributed in the body, occurs in particularly high concentration in bone and cartilage, where it presumably plays an essential part in the process of ossification by producing an excess concentration of phosphate ions which leads in turn to the precipitation of calcium phosphate. The enzyme is present also in the blood serum, where it can be measured by a variety of techniques. Its activity is expressed in arbitrary units, dependent upon the type of substrate employed in the determination. When glycerophosphate is used (Bodansky method) the range of normal for adults is 1.5 to 4.0 units per 100 c.c. of serum. In children the phosphatase activity is increased, ranging between 5 to 12 units per 100 c.c. The enzyme concentration is also elevated in some diseases of the liver, especially those with obstructive jaundice, and in many types of bone disease including rickets, osteomalacia, osteitis fibrosa cystica, and osteitis deformans.[24]

The behavior of alkaline phosphatase in relation to the various phases of reproduction is interesting because of the need for mobilization of phosphorus which the reproductive cycle imposes. This study is divided into four parts: pregnancy, puerperium, lactation, and fetal-maternal relations.

Pregnancy

Pregnancy is associated with a progressive increase in the serum alkaline phosphatase activity. Augmentation is greatest during the last trimester, the highest values being reached at term. This observation, first reported

in 1935 by Cayla and Fabre, has been confirmed by several other investigators.[3, 14, 18, 20, 25, 30] Our data are consistent with these previous reports. Blood was obtained by venepuncture in twenty-six normal women at the time of delivery at term, the serum was promptly analyzed for its alkaline phosphatase activity, and the results expressed in Bodansky units (Table I). The average value for the group (6.32 units per 100 c.c.) was well above the upper limit of normal for nonpregnant women (4 units per 100 c.c.), and all the levels save two exceeded this limit.

TABLE I. SERUM ALKALINE PHOSPHATASE ACTIVITY AT TERM AND IN THE PUERPERIUM

	PHOSPHATASE (BODANSKY UNITS PER 100 C.C.)			
PATIENT	TERM	POSTPARTUM 1 WEEK	POSTPARTUM 4 TO 6 WEEKS	LACTATING
1	6.5	4.3	3.5	No
2	4.2	4.3	4.5	No
3	4.8	4.3	2.8	No
4	3.5	2.7	2.0	No
5	4.8	4.8	5.6	No
6	9.3		3.1	No
7	5.9	6.8		
8	6.3	4.8	3.2	No
9	4.8	3.7		
10	6.8	5.1		
11	8.3	5.2	3.2	No
12	4.8	3.7	2.8	No
13	6.7	4.2		
14	7.6	4.7	2.1	No
15	3.9	2.8	2.0	No
16	9.0	5.6	3.9	No
17	4.8	4.0	2.7	No
18	4.7	5.5	3.6	No
19	7.5	4.3	3.5	Yes
20	5.5	2.6	2.3	No
21	5.7	3.9	5.2	Yes
22	7.4	4.8	2.3	No
23	4.8	3.5	2.4	No
24	7.0	5.5	3.8	No
25	7.4	5.3		
26	11.3	5.8		
Average	6.32	4.48	2.93 (nonlactating)	

The serum phosphatase activities of seven other patients, in the third month of pregnancy, are listed in Table II. These values, which average 2.04 units per 100 c.c., are all within normal nonpregnant limits.

TABLE II. EFFECT OF DIETHYLSTILBESTROL (25 MG. DAILY) ON SERUM ALKALINE PHOSPHATASE

	PHOSPHATASE (BODANSKY UNITS PER 100 C.C.)		
PATIENT	BEFORE TREATMENT	DAYS	AFTER TREATMENT
30	2.8	10	3.7
31	1.9	20	1.4
32	1.6	20	1.3
33	2.1	10	4.6
34	2.2	10	1.9
35	1.6	10	2.0
36	2.1	25	2.4
Average	2.04		2.48

The suggestion that the high estrogen titer of later pregnancy may be responsible for the increase in serum phosphatase seems plausible in view of the fact that another condition in which high phosphatase values often are found, namely hepatic jaundice, is also frequently associated with increased estrogenic activity. This possibility is strengthened somewhat by experimental data. Injections of estrogenic hormone have been shown to produce a marked rise in the serum alkaline phosphatase in lactating cattle[8] and in pigeons,[19] although no significant changes were produced by this means in rats.[5, 21]

Diethylstilbestrol in a daily dose of 25 mg. was given to seven women during the third month of pregnancy in order to determine the effect of estrogens on serum phosphatase in the human being. Such patients seemed well suited to this experiment, because of the tolerance of the pregnant woman to large doses of estrogen and because the normal phosphatase levels are still within the nonpregnant range during the first four months. Duration of treatment varied from ten to twenty-five days. The results are shown in Table II. No consistent change occurred in the phosphatase values. The average increase during treatment (from 2.04 to 2.48 units per 100 c.c.) is not considered significant.

The Puerperium

Blood phosphatase behavior during the puerperium has been the subject of conflicting reports. Hoch and others (1948) have recently recorded a slight increase in the mean concentration of the enzyme during the first week post partum, in disagreement with Vermehren's (1939) observation of an abrupt fall after delivery. They, as well as Meranze and others (1937) and Young and others (1946), have reported a gradual decline of the phosphatase level during later stages of the puerperium in the absence of lactation, although the latter authors found the return to normal nonpregnancy values required six to twelve months, in contrast to the three to four weeks reported by Vermehren.

Repeat determinations of serum phosphatase on twenty-five of our twenty-six patients a week following delivery showed a distinct drop in the enzyme level in all cases but four (Table I). The average value of 4.48 units per 100 c.c. at the end of a week represents a 29 per cent decline from the level at the time of delivery.

A final determination was made in this group of patients at four to six weeks post partum. Of the eighteen nonlactating women who returned for examination, all but two showed a further drop in their serum alkaline phosphatase level. The average value at this point was 2.93 units per 100 c.c., well within the normal limits for the nonpregnant adult. Less than half the average level at delivery, this value represents a further decline of 35 per cent from the average phosphatase activity one week post partum.

Lactation

The puerperal decline in serum phosphatase occurred more slowly in lactating women. Determinations were made on the serum of eighteen such patients at four to six weeks post partum for comparison with an equal number of women who did not nurse their babies. The average value for the nursing mothers was 3.62 units per 100 c.c., a figure 24 per cent higher than the average for the nonlactating mothers. The phosphatase activity in six of the nursing women was greater than 4 units per 100 c.c., whereas in only two of those not nursing was this limit exceeded. The data are plotted in a scattergram (Fig. 1). These findings are in agreement with the observation of

Vermehren that the puerperal return of serum alkaline phosphatase to normal levels within three to four weeks following delivery was delayed in lactating women, who had generally higher values.

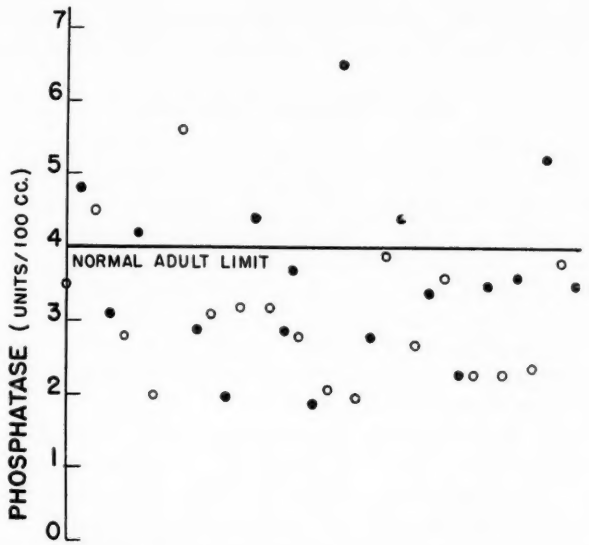

Fig. 1.—Scattergram showing serum alkaline phosphatase values at 4 to 6 weeks post partum. Solid dots indicate women who are lactating; circles, those not lactating.

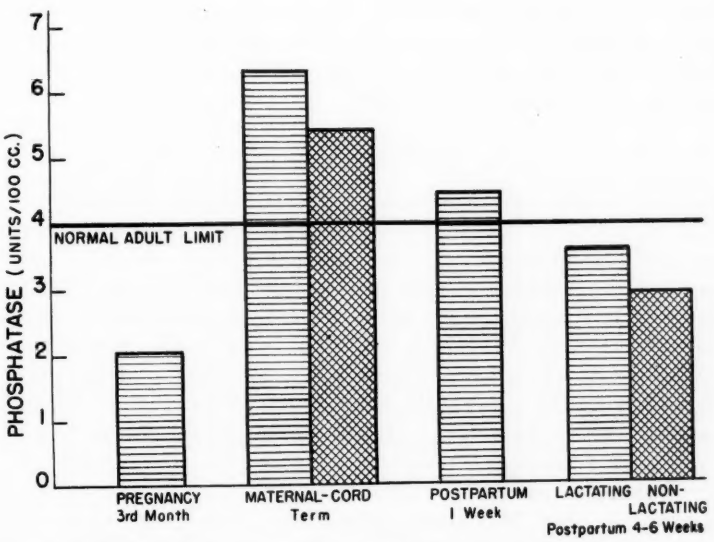

Fig. 2.—Serum alkaline phosphatase relations, showing average values for early pregnancy, term, cord blood, puerperium, and lactation.

It is not surprising that the phosphatase activity is modified by lactation, in view of the large quantities of calcium and phosphate which must be mobilized for secretion by the mammary glands. Experimental evidence supports this concept. Phosphatase in high concentration has been demonstrated both chemically and histochemically in the active mammary glands of lab-

oratory animals.[6, 9, 11] In lactating cattle it is often possible to increase the milk yield by the administration of thyroxine. Folley and White (1936) have observed that increased lactation so produced was accompanied by a coincident rise in the serum alkaline phosphatase. It is uncertain, however, whether the elevated enzyme concentration was related primarily to the injected thyroxine or to the resulting augmentation of lactation. This point could be settled by the use of male or nonlactating female animals.

Fetal-Maternal Relations

Measurements of the phosphatase activity of fetal serum have been made by Stearns and Warweg (1933), by Meranze and others (1937), and by Kerleau and Cayla (1939), all reporting either low levels or normal adult values for the human cord blood at term. These observations are contrary to what one might expect, in view of the intense ossification in progress in the fetus. They are also at variance both with the data of Vermehren (1939), who observed general agreement between maternal and cord blood values, and with the findings in other species. Bodansky (1934), working with puppies, and Young and Underdahl (1948), studying suckling pigs, both reported high phosphatase values in these animals at birth.

We have made simultaneous measurements of the phosphatase levels of maternal and cord serum, both obtained at the time of delivery at term, in twenty-one cases. The results are listed in Table III. The fetal values ranged between 2.9 and 7.9 units per 100 c.c., averaging 5.43 units, or 17 per cent less than the maternal average. The cord levels, however, still averaged distinctly above the normal upper limit for nonpregnant adults. The ratios between the cord and the maternal phosphatase values are listed in the table. In fourteen cases the maternal levels exceeded the fetal; in two cases the values were identical; and in five the cord levels were higher than the maternal. These data indicate that the concentration of alkaline phosphatase in the fetal serum is more or less independent of the maternal and that there is no free passage of the enzyme across the placenta.

Comment

Changes in plasma phosphatase activity seem to occur during pregnancy in other species as well as the human, although these changes are neither constant nor clearly understood. In the albino rat Weil (1941) found the phosphatase level to remain practically stationary through pregnancy, until about six days before parturition, when a marked increase occurred. In pregnant cows and sheep significantly lower values have been reported than among nonpregnant animals[1] although Wilson and Hart (1932) observed considerable variation in the former species, with a rise at the time of parturition.

The assertion that abnormally high phosphatase values are indicative of multiple pregnancies in the human being remains to be verified. Ebbs and Scott (1940) reported levels in six twin pregnancies at term significantly higher than average, but Meranze and others (1937) failed to confirm this in an equal number of cases, nor did Young and others (1946). The highest value reported by Meranze and others, however, was in a patient with triplets.

Varied interpretations have been accorded the pregnancy rise in serum alkaline phosphatase activity. The belief of Kerleau and Cayla (1939) that the high levels in the mother result from placental transmission of the enzyme from the fetus receives little support from our data. No correlation could be made between the maternal and cord serum values. In the majority of instances the maternal level was higher and in only two cases were they identical.

TABLE III. SERUM ALKALINE PHOSPHATASE ACTIVITY OF MATERNAL AND CORD BLOOD AT DELIVERY

PATIENT	PHOSPHATASE (BODANSKY UNITS PER 100 C.C.)		
	MATERNAL	CORD	CORD MATERNAL
1	6.5	3.4	.52
10	6.8	7.9	1.16
11	8.3	7.2	.87
12	4.8	4.2	.87
13	6.7	3.0	.45
14	7.6	7.5	.99
15	3.9	5.1	1.31
16	9.0	4.6	.51
17	4.8	6.1	1.27
18	4.7	6.9	1.47
19	7.5	7.5	1.00
20	5.5	4.2	.76
21	5.7	5.7	1.00
22	7.4	4.6	.62
23	4.8	2.9	.60
24	7.0	6.5	.93
25	7.4	4.9	.66
26	11.3	6.6	.58
27	6.1	6.0	.98
28	6.6	3.7	.56
29	4.6	5.6	1.22
Average	6.52	5.43	

The earlier suggestion by Cayla and Fabre (1935) that augmentation of the phosphatase activity during pregnancy serves as the basis for maternal demineralization in anticipation of fetal needs is attractive and has received some support subsequently from Bodansky and others (1939). These authors have related the progressive rise in phosphatase during pregnancy to an "increased lability of the bone metabolism" of the mother. They have demonstrated in experimental studies on rats that some depletion of the calcium and phosphorus reserves of the bones occurs during pregnancy, especially if the intake of these minerals is inadequate. This demineralization, they concluded, was under control of the parathyroid glands, since rarefaction of the bones was not apparent in parathyroidectomized pregnant rats. The increased activity of the parathyroids during pregnancy, postulated by Bodansky, is supported by histological evidence[22] and by the demonstration in the blood of increased amounts of a substance with the physical, chemical, and pharmacological properties of parathyroid hormone.[12, 15, 16]

The possibility that the pregnancy increase in serum phosphatase is mediated through the rising titer of estrogens is not excluded but receives no support from the present data. Different results might be obtained with longer treatment or larger doses of estrogen.*

Conclusions

1. The serum alkaline phosphatase activity increases during pregnancy. Within normal nonpregnant limits during the first trimester, the phosphatase activity averages a threefold increase by term, thereby exceeding the upper limit of normal nonpregnant values.

*In recent therapeutic trials with estrogens in patients with carcinoma of the prostate (Woodard, H. Q., and Dean, A. L.: J. Urol. **57**: 158-171, 1947) and carcinoma of the breast (Adair, F. E., Mellors, R. C., Farrow, J. H., Woodard, H. Q., Escher, G. C., and Urban, J. A.: J. A. M. A. **140**: 1193-1200, 1949) without osseous metastases, no significant changes in the serum alkaline phosphatase were observed.

2. No significant change was produced in the serum phosphatase levels of a group of women in the first trimester of pregnancy by means of large doses of diethylstilbestrol.

3. The phosphatase activity declines rapidly after delivery and returns to within normal nonpregnant limits by four to six weeks post partum.

4. The puerperal level of phosphatase activity remains slightly higher in women who are lactating.

5. The phosphatase activity of cord blood serum, also above the normal adult upper limit at term, bears no consistent relation to the maternal serum concentration of the enzyme.

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THE BASAL BODY TEMPERATURE OF WOMEN

I. Correlation Between Temperature and Time Factor

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IN ORDER to get the most out of a woman's basal body temperature as a diagnostic procedure in the investigation of infertility and other gynecological endocrine disorders it is imperative that the temperature be taken at the same time early every morning under strictly basal conditions. Advocates of the use of the "waking temperature" (Barton and Wiesner, 1945, and others) without regard for the time factor cannot expect to obtain temperature curves which accurately reflect the effect of the ovarian hormones. Even though regarded as being under basal conditions a woman who awakens late in the morning does not have as low a body temperature at 10 to 11 A.M. as she has at 6 to 7 A.M. Because of diurnal variation the difference between her 6 A.M. and her 11 A.M. temperatures on the same day, even while sleeping continuously, may be as great as or greater than the difference between her "basal" preovulatory and postovulatory temperatures.

This is illustrated by the temperature records in Figs. 1 and 2. Fig. 1 shows the record of a woman's temperature for one complete menstrual cycle taken once daily at 6 A.M. Fig. 2 is the horizontally extended rising temperature section of the curve circumscribed in Fig. 1. The patient was hospitalized for a period of five days during the ovulatory phase of her menstrual cycle for the express purpose of recording her body temperature at hourly intervals from 6 A.M. to 10 P.M. daily. Although she did not sleep soundly and continuously throughout each day she made an effort to do so and at least was at complete rest for a full half-hour before each temperature was taken. (These circumstances are regarded as "basal" as far as basal metabolic rate determinations are concerned.) Thus the patient's body temperature is seen to rise and fall as much or more during each day of observation in Fig. 2 as it is in Fig. 1, the rise in Fig. 1 presumably indicating the approximate time of ovulation.

The diurnal variation in body temperature may be demonstrated more completely perhaps by the continuously recorded temperature of an institutionalized woman reported by Greulich (1946). Fig. 3 shows the mean temperature curve for five consecutive days through its diurnal variation as estimated from the temperature tracings shown in Greulich's report. The curve was plotted on a graph from levels taken from the continuous tracing at hourly intervals. The five-day period of observation was made during the preovulatory phase of the patient's menstrual cycle. Here the amplitude of the diurnal fluctuation is about twice as great as the difference between the mean preovulatory and postovulatory basal temperatures when the latter have been determined from one reading daily taken at the same time each morning (Palmer, 1948). It is ap-

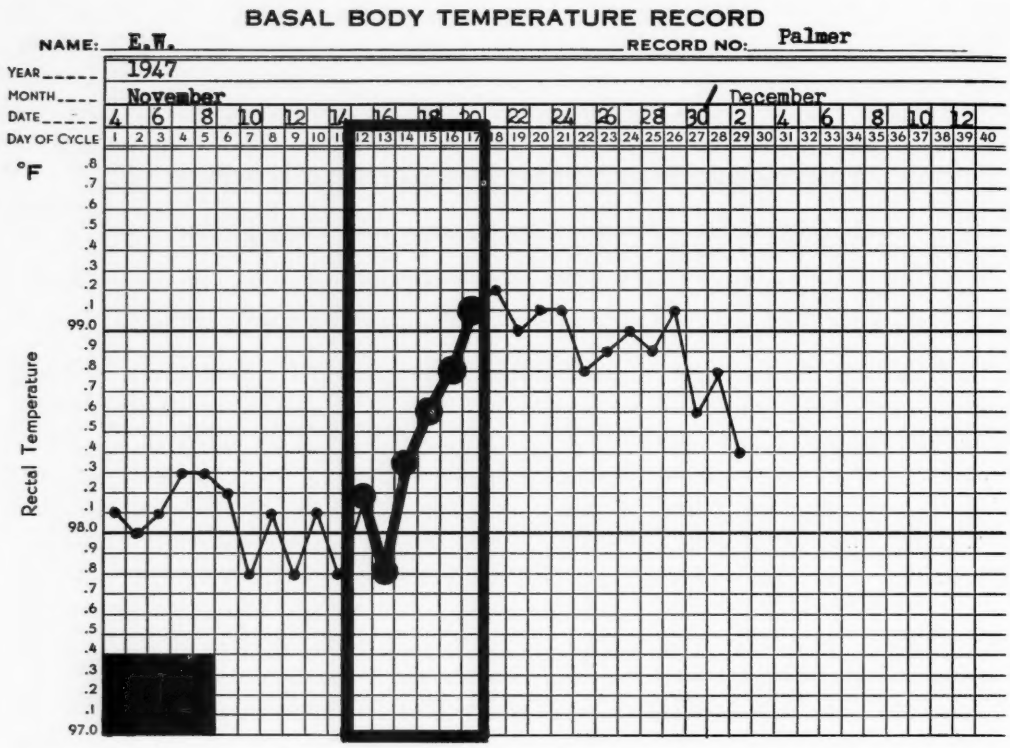


Fig. 1.—Normal basal body temperature curve of a patient during one complete cycle with the temperatures during the thermal shift accentuated.

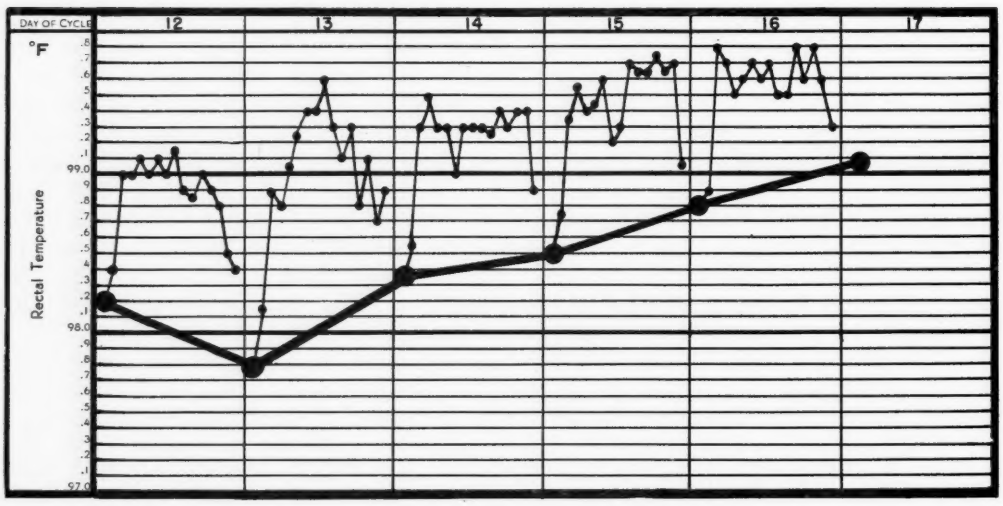
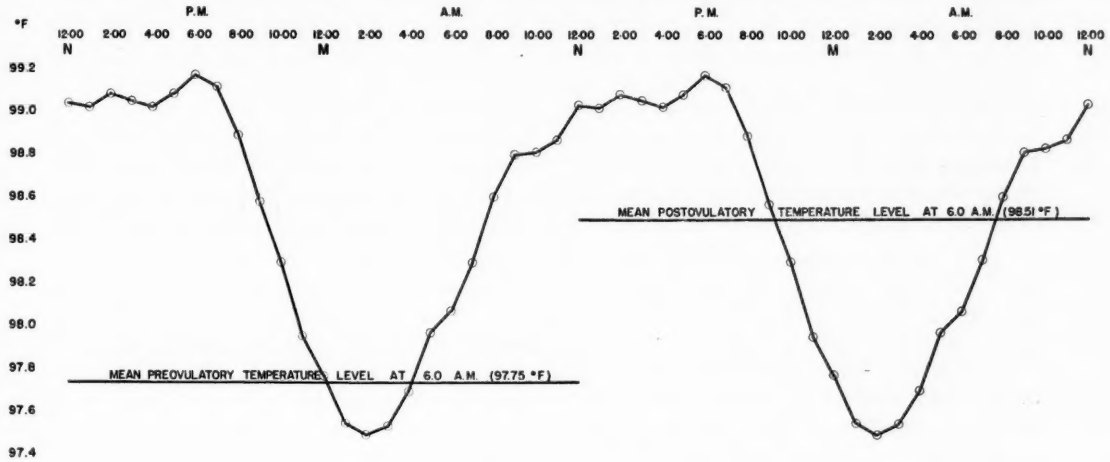


Fig. 2.—Horizontally extended twelfth- to eighteenth-day section of the basal body temperature curve in Fig. 1 to show the variation following the 6 A.M. temperature when taken at hourly intervals until 10 P.M. each day. Note that the temperatures taken after 6 A.M., even though recorded under conditions regarded as basal, show rises during each day which are as high as the "ovulatory rise" of the 6 A.M. temperature.

parent from Fig. 3 that the effects of the ovarian hormones on the body temperature could be completely masked by the diurnal variation of the latter if the time factor were not fully recognized.

A positive significant correlation between the "waking" temperature and the time of day during pregnancy can be demonstrated. It will be remembered that during normal pregnancy a woman's basal body temperature remains elevated, is no longer diphasic, and that its variations from day to day are slighter than at any time during the nonpregnant state. Fig. 4 shows the body temperature of a patient recorded during the seventh and eighth months of gestation. She was an habitual aborter with no living children, this being her fifth pregnancy. She had been instructed to record her basal body temperature throughout her pregnancy in the hope that a threatened abortion or premature labor might be anticipated from the occurrence of a precipitous fall in her basal body



DIURNAL VARIATION OF A WOMAN'S BASAL BODY TEMPERATURE

DURING THE PREOVULATORY PHASE OF HER MENSTRUAL CYCLE

Fig. 3.—Hypothetical curve duplicated as estimated from the continuous basal body temperature tracings reported by Greulich (1946). The mean preovulatory and postovulatory temperature levels have been inserted into the same figure to show these levels as they relate to the diurnal variation. These two levels were calculated from temperatures of twenty-two women during the preovulatory and postovulatory phase of menstrual cycles during which conception occurred (Palmer, 1948).

temperature. Her temperature curve through the sixth month had not been as smooth as it was thought it should have been. In spite of the fact that the patient was taking her temperature presumably at the same time each morning, she was instructed further to record the exact time to the nearest quarter of an hour at which she awakened to take her temperature. The lower curve in Fig. 4 shows the actual variation in time (5:45 to 8:30 A.M.) the patient awakened each morning. The correlation between the two curves is apparent and real as determined by a calculated correlation coefficient of $r = 0.513 \pm 0.094$ ($t = 5.46$, P less than 0.01). The correlation is highly significant.

At first one might think that a correction factor could be used and an interpolated temperature value recorded when a patient takes her temperature at a time at variance with the usual time. However, it must be remembered that while the positive correlation demonstrated in Fig. 4 appears to be a

straight-line relationship for the three-hour period 5:30 to 8:30 A.M., it will be seen from Fig. 3 that a similar relationship does not hold for earlier and later periods. A correction factor, therefore, would have to be a variable one at first increasing and then decreasing before and after the period from 5:00 A.M. to midday, respectively. It is likely also that the high phase of one's diurnal temperature is of longer duration in summer months than in winter months, particularly in north temperate zones where the lengths of the days vary extremely with the seasons of the year.

Several papers have appeared recently on the prediction of the time of ovulation by a urine test on rats (Farris, 1946 and 1948a, and Murphy and Farris, 1947 and 1948). The most recent paper on the subject (Farris, 1948b) could lead to enthusiastic acclaim and acceptance of the method he proposes for detecting the time of ovulation in the human being. A high percentage of disagreement was observed between the time of ovulation as predicted by the rat test and the time of ovulation as estimated from the patient's basal body temperature record. Such reports could also lead to widespread rejection of the use of basal body temperature as a means of investigating ovulation and various gynecological endocrine disorders associated with the presence or absence of ovulation. Cary (1948) has reported unfavorably on the use of the basal body temperature as a guide for estimating the time of ovulation. Other workers (Palmer and Devillers, 1939a, Palmer, 1942, Barton and Wiesner, 1945, Greulich, 1946, Buxton, 1947, and others) have been unable to agree as to the exact time ovulation occurs with respect to the "thermal shift" during the menstrual cycle.

In the first place it should be pointed out that those who have claimed that the "thermal shift" of the basal body temperature during the midintermenstruum is due to ovulation, or that the exact day of ovulation can be determined from the basal body temperature curve probably have taken too much for granted. On the other hand, however, it has been proved that the variations in the basal body temperature of the normally menstruating woman are due to the actions and interactions of the two principal types of ovarian hormones, estrogen and progestogen (Palmer and Devillers, 1939b, and others). Basal body temperature curves which appear to be normal can be reproduced in the human female castrate by the proper cyclical use of these two types of hormones. Obviously no "ovulation" could occur in the castrate. Therefore the upward thermal shift of the basal body temperature of women should be regarded generally as evidence of the onset of corpus luteum formation and/or progestogen activity rather than specifically ovulation as characterized by mechanical rupture of a mature Graafian follicle.

Since fluctuations of a woman's temperature are produced by the action and interaction of the two types of ovarian hormones it is logical to suppose that her basal body temperature record could be used diagnostically as a means for the investigation of her ovarian function. And since it is known that the production of progestogen does not occur until after the Graafian follicle begins to be luteinized many have assumed that the thermal shift of the basal body temperature indicates the simultaneous occurrence of ovulation and onset of progestogen production. If progestogen were never produced until the time of follicle rupture this assumption would be correct.

The exact relationship between the time of follicle rupture and the onset of progestogen production is not known. It probably varies. Evidence has been accumulating which indicates that some degree of luteinization and the production of a progestogen may occur before or in the absence of follicle rupture. Such evidence includes the occurrence in the medical literature of approximately ninety cases of true ovarian pregnancy by the criteria of Spiegelberg (1878), occurrence of "anovulation with progestational transformation of

the follicle'' (Stieve, 1926; Cotte and Pallot, 1935; Dubreuil, 1944a and b; Culiner, 1945; Schockaert and associates, 1946; Schockaert and Ferin, 1946), the observation by Greulich (1946) that the basal body temperature may rise prior to follicle rupture, the suggestion of luteinized follicles with trapped ova and ''immature'' progestational endometrium associated with ovulatory failure (Hamblen, 1947, and Abarbanel, 1947), and the suggestion of mechanical failure of ovulation (Palmer, 1948). It is possible also that a follicle may rupture a few days prior to the beginning of luteinization. Follicle rupture might be provoked by the act of sexual intercourse a few days earlier than it might normally have occurred, followed by some delay in the onset of luteinization.

Farris (1948b) reports that conception frequently takes place on the date of intercourse and that that date is occasionally several days prior to the rise of the basal body temperature. However, it is probably erroneous to conclude that conception always occurs on the one day during which an isolated insemination is performed or sexual intercourse takes place. Normal spermatozoa have survival times of at least twenty-four hours and have been found actively motile in cervical secretions as late as five days after isolated coitus. Coitus on any one of several days after the date noted in most of the temperature records reported by Farris might also have resulted in conception. Although intercourse between the couples under investigation was interdicted during each testing period no statement is made as to the frequency of intercourse thereafter.

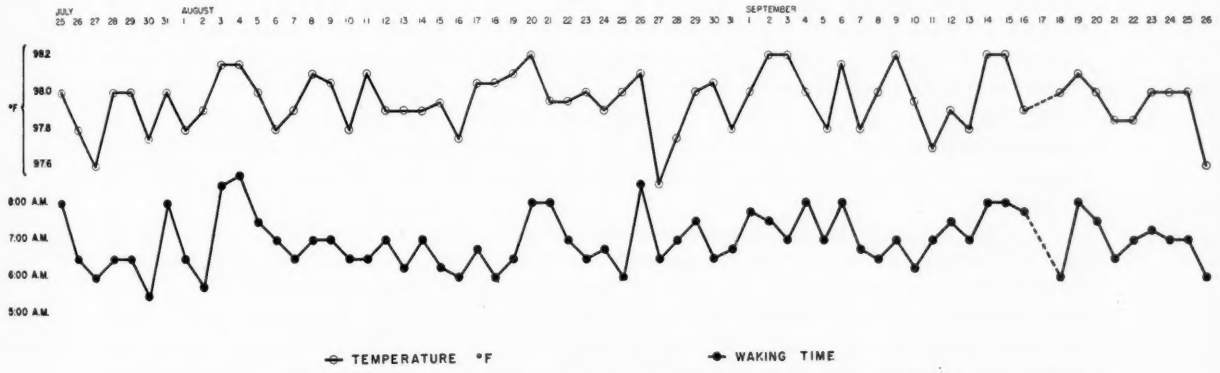


Fig. 4.—The correlation between body temperature and "waking" time in a patient during the sixth and seventh months of gestation.

It would be of interest to determine in the cases presented with basal body temperature curves (Farris 1948b) just how early and by what means the diagnosis of pregnancy was confirmed. One of his patients in particular, No. 5, Fig. 1, was assumed to be pregnant and the body temperature record shows a subsequent fluctuation similar to that which occurs in a normal menstrual cycle. There is no indication whether or not there was any bleeding associated with the fall of the basal body temperature subsequent to the diagnosis of pregnancy. Zuck (1938) reported a similar observation in which a complete diphasic fluctuation and presumably menstrual flow occurred after the onset of pregnancy.

The body temperature curves illustrated by Farris show rather marked fluctuations from day to day suggesting that they may not have been taken under strictly basal conditions. Some of them are generally low and some generally high indicating that possibly some were rectal and others oral or axillary temperatures. Other reasons for day-to-day variations in the body temperature could be the change of thermometer from time to time by the individual patient, and failure to adhere strictly to the same time each morning for taking the temperature.

According to Farris the body temperature records associated with the onset of pregnancy in twenty-seven patients show that from two to fifteen days were required for the temperature to rise to its highest point. This need not necessarily mean that that period of time was required for a significant elevation of the temperature to occur. An analysis has been made of the basal body temperatures of twenty-two women recorded during the cycle in which conception occurred (Palmer 1948). Without any regard for the exact day coitus or insemination resulted in the onset of pregnancy (i.e., the date on which the incident took place with respect to the change in the basal body temperature), the average type of temperature curve showed a statistically significant elevation, characteristic of menstrual cycles during which follicle rupture must have occurred as proved by pregnancy, in twenty-four hours. The highest level of the temperature was not actually reached until some days later, but at least the elevation was abrupt and significant in the first twenty-four hours after it began to rise. An explanation for the failure of the temperature records of the twenty-seven pregnant women reported by Farris to show an abrupt temperature shift in twenty-four hours is the possibility that his patients were not instructed or did not follow the instructions to adhere strictly to basal conditions.

A point might be made about the greater advantage of the Centigrade over the Fahrenheit thermometer for taking the basal body temperature. Most clinical Fahrenheit thermometers show divisions of 0.2 of a degree and it is difficult for one unaccustomed to reading a thermometer to make an accurate reading. Centigrade thermometers, on the other hand, particularly the newly produced basal temperature thermometers by the Arveson Thermometer Corporation (''Arteo Cycletemp''), have a division for every tenth of a degree Centigrade; the divisions are quite wide apart and they are very easy to read. Patients being studied by the basal body temperature method should be urged to procure a Centigrade rectal thermometer. And, incidentally, statistical calculations on values in the neighborhood of 37 are easier to handle than values of the order of 98 and 99.

Farris reports days eight to nineteen of the cycle as the range within which ''conception'' has occurred in his series. The thermal shift of the basal body temperature in twenty-two women at the onset of pregnancy referred to above was observed to occur from the tenth to the thirtieth day of cycles which presumably would have been from twenty-three to forty-three days in length had not pregnancy supervened (Palmer, 1949). This range is at least twice as great as that reported by Farris. Tompkins (1946) also reports a wide range for ten sterility patients of from twelve to eighty-two days as confirmed by date of delivery of the term infant. So great a range explains the statements made so frequently to the effect that conception may occur on any day of the cycle.

Summary and Conclusions

The body temperature of women has been shown to have a diurnal variation sufficiently great to obscure completely the diphasic fluctuations of her basal body temperature if the time factor is not fully recognized. The basal body temperature when taken early and at precisely the same time every morning may be expected to reveal quite accurately, if not quantitatively, the occurrence of the estrin and progestin phases of the ovarian cycle in relation to the menstrual cycle. The cause and effect relationship between the two types of ovarian hormones and the diphasic basal body temperature has been established. Variation from the normal basal body temperature curve when properly recorded is evidence of abnormal ovarian function.

It is not always possible to determine accurately the exact day or time of ovulation from the basal body temperature curve, since it has been shown that progesterone which is known to effect an elevation of the basal body temperature may be produced prior to or in the complete absence of follicle rupture. And further, the possibility has been suggested that progesterone production occasionally may not begin until some time after follicle rupture as well.

The thermal shift of the basal body temperature is an indicator of the approximate time of ovulation if and when the latter is known to occur but as has been stated by Barton and Wiesner (1945) it should be remembered that the change in the basal body temperature at the midintermenstruum may be regarded as evidence but not proof of mechanical rupture of a mature Graafian follicle.

And, last, the absence of diphasic basal body temperature is unmistakable evidence of the failure of ovulation.

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2107 VAN NESS AVENUE.

ADENOCARCINOMA IN ONE HORN OF UTERUS DIDELPHYS*

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THE incidence of congenital malformation of the genital tract is undoubtedly much more common than is appreciated. Many of the abnormalities are discovered only during the course of an investigation for infertility, during an exploratory laparotomy for an undiagnosed condition, during pregnancy, or at autopsy.

The coexistence of malformations of the uterus and corpus carcinoma, although probably a coincidence is, however, relatively rare and its existence in a uterus didelphys even rarer.

Von Franqué[1] in 1930, after a careful review of the world literature since 1777, reported twenty-three cases of uterine carcinoma coexisting in uterine anomalies. Of these nine were fundal and fourteen were cervical carcinomas. Of the nine, only two were found to be in one horn of a uterus didelphys. The first case was reported by Hofmeier[2] in 1902 of a carcinoma in the right horn of a uterus didelphys, in a woman, aged 51 years, diagnosed at autopsy. The second was that of Brandes,[3] reported in 1925, of a squamous-cell carcinoma in the left horn of a uterus didelphys in a 54-year-old woman, diagnosed at laparotomy. The third was that of Reimer[4] who reported in 1934 a corpus carcinoma in one horn of a uterus didelphys, which had penetrated through and infiltrated the opposite horn and vagina. This was diagnosed at autopsy. To this is added another case of corpus carcinoma in the left horn of a uterus didelphys.

This case is of interest for the following reasons: first, it occurred in a relatively young woman, aged 29 years; second, it was discovered during an investigation for infertility; third, because of its rarity.

Although not directly applicable to this case, may I parenthetically state that we have been able to discover, with the aid of endometrial biopsies, three other cases of corpus carcinoma in women under the age of 30 during infertility investigations. All of these were subsequently operated upon and the diagnosis of adenocarcinoma of the fundus confirmed. It has been our practice to do endometrial biopsies in our infertility problems, particularly when the hysterosalpingograms show uterine malformations or fundal irregularities, about ten days following such examination and not at the first day of menses, for we feel that biopsies taken on day one of the menstruation do not give accurate interpretations of the endometrial pattern. The endometrial tissues at this time are ischemic, partially necrosed or in some regions necrotic and may be partially or completely inactive functionally. Such endometrium does not reflect functional corpus luteum activity. Brewer and Jones[5] and Bartelmez[6] found these changes occurring a day or two prior to the onset of menses.

Case Report

A 29-year-old white woman was referred to us in June of 1944 for an investigation of her sterility of eight years' duration. She had been married for 10 years. Past family and childhood histories were not significant. Catamenia commenced at 14 years, of the twenty-

*Presented at a meeting of the Brooklyn Gynecological Society, Nov. 5, 1948.

eight-day type, bleeding was moderate for seven days with occasional small clots and no dysmenorrhea. During the past five or six years she had often spotted, without pain, a day or two between periods, not necessitating the use of a napkin. There was a mild, nonodorous discharge which she did not consider abnormal. Her sex life was satisfactory, having coitus about three times a week without dyspareunia. In 1941 the patient consulted a physician for her sterility. A dilatation and curettage were performed, and in 1942 another dilatation and curettage were done to promote "fertility." Reports from the hospital where these two operations were done revealed that no gross pelvic abnormality was found and that, histologically, the endometrial curettings showed normal endometrium. It is quite possible that only one horn, the right, had been curetted, for the vagina on the right side was the larger and more patulous of the two. As a matter of interest, the husband did not at any time note any interference in his intromission, and he was indeed surprised when apprised of the abnormality under discussion. Her status was that of a well-developed, well-nourished, white woman with normal secondary sex characteristics, weight 143½ pounds, height 65 inches. Abdominally, there were no masses or tendernesses present. Vaginally, the vulva, urethra, Skene's and Bartholin's glands were normal. There was a complete vaginal septum dividing the vagina to the cervix. The right was more patulous and larger than the left, the latter being constricted and admitted one finger, but, however, was dilatable. The cervices were both visualized, the portio of the left being larger than the right. Both cervices were elongated and freely moveable. The uterus was of normal consistency and position, but about one and a half times larger than normal and a cleft could be palpated dividing the fundus. Adnexa were not defined. A diagnosis of congenital malformation of the uterus was made.

Fig. 1.—Didelphys uterus with adenocarcinoma of the left fundus.

Subsequent hysterosalpingograms showed two distinct vaginal canals, cervices, and uteri. The left uterus was larger than the right, the mesial border being irregular in outline and saw-toothed in appearance. There were several filling defects in its cavity. The right uterus, although underdeveloped, was normal in outline. Both of the cervices were elongated, both tubes were visualized, the left being adherent posteriorly and terminating at its fimbriated end in hydrops formation. The right tube was normal and patent (Fig. 1). In view of the architecture of the left uterus, intrauterine pathology was suspected, either endometrial polypi, fibromyoma, or malignancy.

Endometrial biopsies, taken on July 11, 1944, from each horn were reported as follows: The tissue from the right horn showed an endometrium that was thickened. The glands were round or tubular, lined by multiple layers of columnar epithelium with oval or round nuclei at various levels. The surrounding stroma was compact, the stroma cells were darkly stained, had little or no cytoplasm; and there was an extravasation with erythrocytes. Some of the nuclei were hyperchromatic, and showed an occasional mitotic figure. Diagnosis: Normal proliferative endometrium.

Endometrial tissue of the left horn showed a tumor with papillary projections and glandular formations. These projections were quite large and were covered by multiple layers of endothelial cells varying in size, shape, and staining qualities, have hyperchromatic nuclei with an occasional mitotic figure. The stromas of these papillary projections were infilfrated with these neoplastic cells in various portions. The glandular elements were markedly increased in number, varied in size and shape, and some had undergone a slight dilatation. The lining epithelium was quite similar to that covering the papillary projections. Some of the glands were imperfectly formed and their lumina were filled with neoplastic cells. The intervening stroma was reduced to narrow strands of connective tissue and an occasional island of neoplastic cells was present (Fig. 2). A diagnosis of papillary adenocarcinoma of the left horn was made and the patient advised that a thorough diagnostic curettage should be done and if diagnosis was conclusive further surgery would be necessary. This advice was not followed.

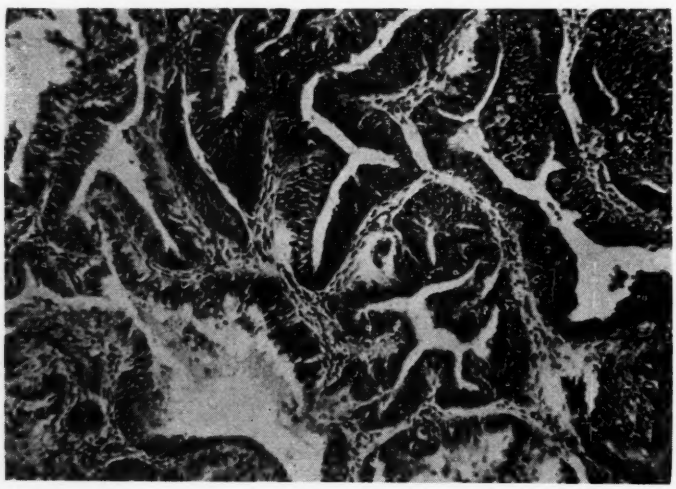

Fig. 2.—Endometrial biopsy in 1944, from left horn. Papillary adenocarcinoma. (×100.)

The patient was not seen again until May 2, 1946. Her menstrual history had not changed except that bleeding was somewhat more profuse. Her weight was 146 pounds and she seemed in fairly good health. At this time, vaginal smears were taken and biopsies repeated.

The smear from the right revealed normal cytology. The smear from the left, mainly from the portio and endocervix, contained a large number of leucocytes, red blood cells, and histocytes. Many of the histocytes were clumped. There was a preponderance of intermediate and deep cells with relatively few cornified epithelial cells of the superficial layer. There were a number of endometrial cells seen that showed pyknotic hyperchromatic, enlarged and irregularly shaped nuclei, some of which showed the chromatin material arranged in thick groups and in other areas were giant cells showing vacuolization and deeply stained nucleoli. This smear was regarded as positive for adenocarcinoma of the corpus (Fig. 3).

Endometrial biopsies taken the same day revealed the following: The histopathology of the endometrial curettings of the left horn differed from that of 1944 in its cellularity. This was much more anaplastic. The papillary projections and glandular elements were made up of darkly stained cells due to the marked amount of hyperchromatosis of the nuclei and there were present also a moderate number of mitotic figures. The stroma of the papillary projections and the stroma of the glands showed infiltration with tumefaction cells. In many portions of this tumor, the stroma was reduced to narrow strands of connective tissue. Many of the glands were imperfectly formed (Fig. 4). The endometrial biopsy of the right horn again showed a normal proliferative endometrium.

All of these histological slides and smears were submitted to three general and three gynecological pathologists. There was unanimity of opinion as to a diagnosis of adenocarcinoma of the left horn from all but one, who stated that from a histological standpoint

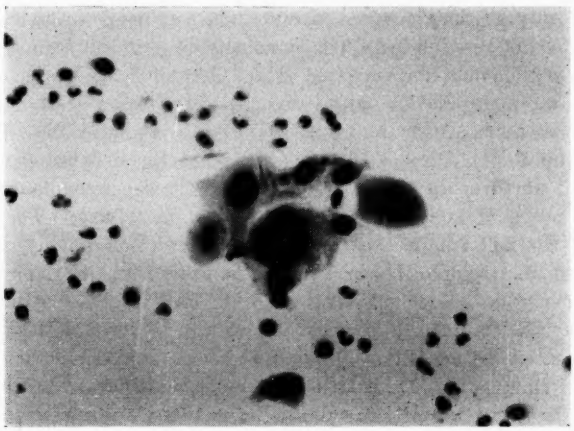

Fig. 3.—Smear from left endocervix in 1946. A group of malignant endometrial cells showing anisokariosis. There are other suspicious single cells. (×460.)

Fig. 4.—Endomentrial biopsy in 1946, from left horn. Papillary adenocarcinoma, more anaplastic than that of Fig. 2. (×230.)

they represented a sort of borderline, atypical pseudomalignant condition of the endometrium, although he believed it to be benign, representing an unusual degree of a gross response to the estrogenic hormones. In view of the majority of opinions, a panhysterectomy was performed on June 8, 1946. There were no parametrial fixations. The patient made an uneventful recovery, out of bed on the second postoperative day, and discharged on the tenth postoperative day. The patient was again seen in November, 1947, and in June, 1948. Her weight was 147 to 153 pounds, and she appeared in good health. Vaginal examination showed no indurations or parametrial involvement, no vaginal bleeding.

The specimen consisted of a complete uterine mass, two uteri, and two cervices uteri. The uterine mass measured over-all 8 by 3 by 4 centimeters. The uterine bodies were separate

at the fundus. Both cervices presented independent, external openings, edges, and external canals. When the uterine canals were opened, each was found to be about 8 cm. in length and uniform throughout. No communication between the two canals was evident. The two cervices were united only at their surface layers. The endometrial cavity of the right uterus was moderately dilated at the fundus. The endometrium was uniformly thin and flat up to the fundus. Here the endometrium appeared thick, irregularly polypoid or papillary. It was found to be pliable on manipulation with forceps. Transverse section of the endometrium showed a sharp line of demarcation with the underlying myometrium. The left endometrial cavity was uniform up to the fundus where it appeared to be definitely dilated. The endometrium was flat and uniform up to the fundus. Here it was irregularly thick and appeared ragged. Numerous polypoid structures projected into the cavity. They broke off readily. The endometrium of the left fundus was much more thick than that of the right fundus, and on transection showed an irregular basement membrane with an incomplete demarcation from the underlying myometrium. Each structure had its own adnexus attached at the external pole. Each adnexus was completely formed. Both tubes were of average size and shape. The right ovary measured 2.5 cm. in length and presented a cystic structure in its outer pole 1 cm. in diameter. On section, transparent jellylike material was seen. A small corpus attriticum was also present. One or two minute transparent cysts were present in the ovarian stroma near the large cyst. The left adnexus consisted of a tube and an ovary. The tube resembled the right tube closely. The left ovary was ovoid in shape and on section showed several gelatinous cysts. A small focus of dark brown necrotic material was also seen.

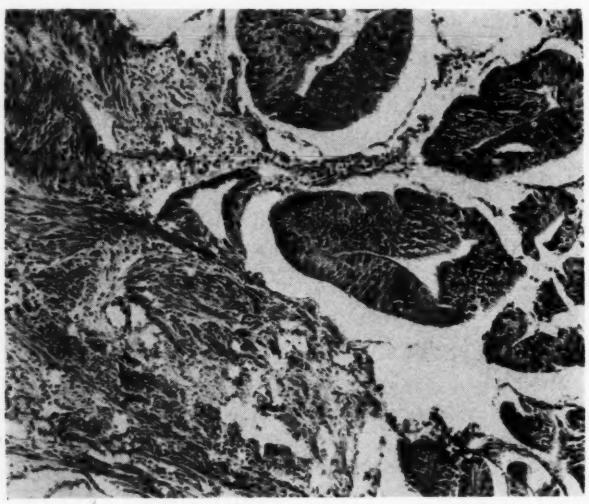

Fig. 5.—Section of uterine wall of left fundus. Papillary adenocarcinoma. (×100.)

Microscopically, the endometrium in the right uterus showed medium-to-large glands, some showing beginning cystic proportions. The lining epithelium was cylindrical, tall and broad. The nuclei were greater than the cytoplasm which was solid in staining. Slight vacuolization was seen in an occasional gland. The endometrial stroma was cellular, the fibroblasts being large, ovoid, and consisting chiefly of nuclei. Mitotic figures were present in both the epithelium and fibroblasts. Diagnosis: Endometrial hypertrophy and hyperplasia.

The endometrium of the left uterus was completely sectioned. Everywhere the sections showed marked fibroglandular hypertrophy and hyperplasia with active mitosis. Giant acini or papillary structures were observed. Microscopically, the basal layer of the endometrium was irregular in its outline with invasion or spilling over into the stroma and musculature. There was a marked anaplasia of the cells of the glands with considerable hyperchromatosis and mitosis of the nuclei (Fig. 5).

Microscopically, all the cysts of the ovaries noted grossly showed many layers of granulosa cells lining the membranes. One or two cysts showed hemorrhagic infiltration. Theca-cell hyperplasia was present in others. The dark, brownish, granular mass was old blood clot (degenerating old hemorrhagic corpus luteum). Both cervices, on section, showed characteristic cervical fibroglandular tissue and a few small- to medium-sized mucous cysts were seen embedded in the cervical stroma. Microscopically, there were numerous glands present, all appeared to be lined with tall, broad, cylindrical epithelium, the cells containing abundant mucus; the stratified epidermis present showed no major changes. A few foci of subepidermal lymphocytic infiltration were present together with periglandular cell infiltration in some of the glands. In one cervix uteri a rather large microscopic focus of intense eosinophilic leucocytic infiltration was present.

Final diagnoses, both gross and microscopic were as follows:

1. A complete uterus didelphys.
2. Hyperplasia of the endometrium of the right horn, late proliferative stage.
3. Papillary adenocarcinoma of the left horn.
4. Multiple granulosa- and theca-cell cysts, bilateral.
5. Fibroglandular hypertrophy of both cervices with cyst formation.

Summary and Conclusions

1. The coexistence of malformation of the uterus and carcinoma is probably a coincidence. One might assume, however, that the endogenous estrogen produced by the diffuse granulosa- and theca-cell hyperplasia of the multiple cysts present in the ovaries in this case was responsible for the hyperplasia of the endometrium in both horns. The development of carcinoma in one horn suggests the probable importance of the genetic factor[7] in creating tissue susceptibility to abnormal growth stimuli, with resultant malignant metaplasia of the atypical endometrium. The relationship of hyperplasia and the development of adenocarcinoma of the endometrium is still to be definitely established.

2. A rare case of carcinoma in one horn of a uterus didelphys is presented in a young woman, 29 years of age. To our knowledge this is the fourth such case reported.

3. Biopsies of the uterus and vaginal smears should be taken prior to day one of the menses in all cases that present irregularities in the architecture of the uterus as demonstrated by hysterosalpingography. Carcinoma may be diagnosed early by such means in a limited number of asymptomatic women in whom it would have otherwise escaped detection.

I wish to thank Drs. M. J. Fein and W. E. Youland, pathologists of the Unity Hospital, for their descriptions of the specimens and for the histological preparations and interpretations. My thanks are also extended to Drs. Shields Warren, A. T. Hertig, E. Novak, and C. E. Folsome for their valued opinions of the histological sections submitted to them.

Many of the illustrations are deleted for lack of space.

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THE BACTERICIDAL ACTION OF BETA PROGESTERONE

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IN A study of bacteriologically proved and clinically suspected cases of acute gonorrhea it was shown by Koch, 1947, that negative cultures are associated with the luteal phase of the menstrual cycle, when progesterone activity and acidity of the cervical mucus are at their height. Swartz, Shohl, and Davis, 1920, proved the acid-death point of the gonococcus, in vitro, to be pH 6.6. On the basis of the above data experiments were made to determine whether or not pure crystalline beta progesterone would have any effect upon the viability of the gonococcus in vitro, if incorporated in a medium adjusted to a favorable pH for growth of the organism, and in a slightly acid medium. Other members of the Neisseria and representatives of the gram-positive and gram-negative organisms were also included in this study.

In 1943, Faulkner made an extensive in vitro study of the effect of estrogens upon a group of organisms and concluded that diethylstilbestrol was bactericidal and in a lesser concentration bacteriostatic to the gram-positive cocci, *Corynebacterium diphtheriae* and *Neisseria catarrhalis*. No inhibitory action was obtained upon the growth of gram-negative bacilli. The minimal lethal concentration varied between 1:5,000 and 1:50,000. Estrone, estradiol, and diethyloxytriphenolbromoethylene did not have any bactericidal action. Sabatelli, 1946, reported that high doses of "folliculin" (16 and 32 I.U. per 10 ml. of ascitic agar) have an inhibitory action upon the growth of the gonococcus in vitro, but no mention was made of the specific estrogenic hormones used. Koch, 1947, was unable to obtain any inhibition of growth of the gonococcus using concentrations of 1:5,000 and 1:10,000 of pure crystalline alpha estradiol incorporated in pancreatic digest broth pH 7.4.

Methods

Due to the excellent results obtained by using pancreatic digest media of Brown, 1948, for the isolation of the gonococcus from cervical cultures and for the cultivation of pure cultures (Koch, 1946, 1948), pancreatic digest broth and pancreatic digest chocolate blood agar were used exclusively throughout the course of this investigation. All media were carefully adjusted to pH 7.4 and pH 6.8.

Pure crystalline beta progesterone was prepared in ether solution in multiple dilutions of 0.1, 0.01, and 0.001 per cent. Measured amounts of these dilutions were added to tubes of broth so that a 5.0 ml. volume contained the final desired dilution after incubation in a 56° C. water bath for 30 minutes to evaporate off the ether.

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Each tube was inoculated with 0.1 ml. of a 24 hour broth culture of the test organism and immediately incubated at 37° C. After 30 minutes, 24, and 48 hours, 0.1 ml. was transferred to respective chocolate blood agar plates which were spread and incubated at 37° C. After 24 and 48 hours extent of growth was determined by colony counts. All plates were incubated aerobically except those inoculated with *Neisseria gonorrhoeae* and *Neisseria intracellularis*, which were incubated in an atmosphere containing approximately 10 per cent carbon dioxide.

Controls consisted of cultures of all test organisms made in broth omitting the substance being tested, but containing a volume of ether equal to the maximum volume used in the experimental series, and evaporated off in the same manner as in the test proper.

The group of organisms tested comprised the following: Nine freshly isolated strains of *Neisseria gonorrhoeae*; two strains of *Neisseria intracellularis*, Strain 1 an old laboratory strain and Strain 2 recently isolated from the spinal fluid of a 13-year-old boy having meningococcus meningitis. A laboratory strain of *Neisseria catarrhalis* and a strain of *Neisseria sicca* isolated from the blood of a patient with a diagnosis of subacute bacterial endocarditis. The gram-negative organisms tested were *Proteus vulgaris* and *Escherichia coli*. The gram-positive organisms were *Staphylococcus aureus, Streptococcus fecalis, Corynebacterium diphtheriae, Corynebacterium pseudodiphthericum*, and *Corynebacterium xerose*.

Results

Beta progesterone incorporated in broth pH 7.4 has bactericidal activity to *Neisseria gonorrhoeae* in dilutions ranging from 1:20,000 to 1:30,000; to *Neisseria intracellularis* in dilutions from 1:20,000 to 1:40,000; and is bacteriostatic to *Neisseria catarrhalis* in a concentration of 1:10,000. It had no inhibitory action in any dilution, upon the growth of *Neisseria sicca* (Table I).

In an investigation of the effect of low pH upon the viability of the gonococcus in vitro, growth in broth adjusted to pH 6.8 was reduced approximately 50 per cent as compared with growth in broth pH 7.4. Progesterone incorporated in broth pH 6.8 was bactericidal to the gonococcus in a concentration of 1:1,000,000.

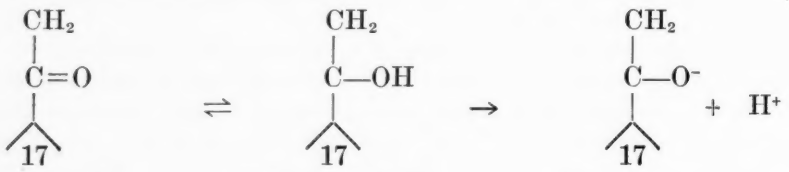
Progesterone in dilutions ranging from 1:10,000 to 1:100,000 had no inhibitory action upon the growth of the gram-positive and gram-negative organisms tested.

TABLE I. EFFECT OF PROGESTERONE UPON THE VIABILITY OF MEMBERS OF THE GENUS NEISSERIA

ORGANISM	DILUTIONS SHOWING NO GROWTH AFTER INCUBATION, 37° C.	
	24 HOURS	48 HOURS.
Neisseria gonorrhoeae		
Strain 1	1:20,000	1:20,000
Strain 2	1:30,000	1:20 000
Strain 3	1:30,000	1:30,000
Strain 4	1:20,000	1:20,000
Strain 5	1:20,000	1:20,000
Strain 6	1:30,000	1:20,000
Strain 7	1:30,000	1:30,000
Strain 8	1:30,000	1:20,000
Strain 9	1:20,000	1:20,000
Neisseria intracellularis		
Strain 1	1:50,000	1:40,000
Strain 2	1:40,000	1:20,000
Neisseria catarrhalis	1:10,000	—
Neisseria sicca	—	—

Discussion

Any attempt at an explanation of the bactericidal action of beta progesterone upon certain of the Neisseria would be entirely speculative. It is a diketo tetracyclic crystalline steroid having the empiric formula $C_{21}H_{30}O_2$. It possesses a keto-acetyl group at C_{17} which may, in alkaline medium, undergo tautomerism by migration of the H of the adjacent C atom to the carbonyl group, favoring an excess of the enol form. The hydroxyl group of the enol form might then dissociate into an anion and a H ion, suggesting that the ionized form is better able to penetrate the cell wall and interfere with the normal cellular metabolism, than the unionized form.



keto-acetyl form enol-acetyl form anionic form

The minimal lethal concentration of progesterone, incorporated in broth pH 7.4, for the gonococcus and meningococcus is 1:20,000. This dilution represents 0.25 I.U. per 5.0 ml. broth. An international unit is the activity of 1.0 mg. of an international standard preparation of beta progesterone, one mg. being the minimum quantity necessary to produce +++ proliferation in sexually mature recently castrated rabbits. When incorporated in broth pH 6.8 a concentration of 1:1,000,000 is lethal for the gonococcus; however, it must be remembered that most strains of this organism are normally susceptible to even slight changes in reaction on the acid side of the pH scale.

It is not possible to correlate the effect of the concentration of progesterone upon the viability of the gonococcus in vitro, with the effect upon the viability of the organism in vivo. First, the concentration of progesterone in the cervical mucus, during the luteal phase of the menstrual cycle, has not been determined. The activity of the corpus luteum is not measured by the activity of its biologically active hormone progesterone, but by the excretion, in the urine, of its biologically inactive metabolite, pregnandiol. Venning and Browne, 1937,[5] found that the maximum amount of pregnandiol (as sodium pregnandiol glucuronidate) excreted during the luteal phase is 5.0 mg. per day. Second, during progestational activity the acidity of the cervical mucus is below pH 6.6, the acid-death point of the gonococcus, and this in itself would be lethal for the organism.

Conclusions

In alkaline medium beta progesterone is bactericidal and in lesser concentrations bacteriostatic to the gonococcus and meningococcus. In slightly acid medium it is bacteriostatic to the gonococcus in much lower dilutions.

Beta progesterone has no inhibitory action upon the growth of *Neisseria sicca* nor upon the growth of gram-positive and gram-negative organisms more or less commonly encountered in the genitourinary tract.

Acknowledgment

The author wishes to thank Dr. J. Howard Brown for his constructive criticism during the course of this investigation and Dr. Georgianna Seegar-Jones for making available the pure crystalline beta progesterone.

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Bradbury, J. T., and Brown, W. E.: Absorption and Excretion of Chorionic Gonadotropin Administered Intramuscularly in Women, J. Clin. Endocrinol. **8**: 1037, Dec., 1948.

A study of the absorption and excretion of chorionic gonadotropin was made after it had been shown that daily doses of 10,000 I.U. of this hormone prolonged the life of the corpus luteum in women and that the urinary excretion of the gonadotropin was sufficiently high to give a positive Aschheim-Zondek reaction.

Ten thousand international units of chorionic gonadotropin in one of three different types of solution were given to women as a single intramuscular injection. The three solutions were aqueous, an emulsion of oil and cholesterol (Emulgen), and an oil and wax mixture. Successive twelve-hour urine specimens were then collected for periods of forty-eight to one hundred twenty hours and the concentration of chorionic hormone assayed by injection into immature female rats. The endpoint was determined by the presence or absence of corpora lutea in ovaries of the rats ninety-six hours later. Because 3 c.c. of urine (1 c.c. daily) gave inconsistent results, dosage was reckoned in volumes representing one, three, and six minutes of urinary output. With three-minute output volumes, chorionic gonadotropin was uniformly present in the urine as long as forty-eight hours after injection of the hormone, irrespective of the medium used. Ninety-six- and one hundred twenty-hour periods were then observed. After an injection with aqueous solution of gonadotropin, 1 rat unit was excreted each three minutes after six to twelve hours increasing to 1 rat unit every one to two minutes from the twenty-fourth to the forty-eighth hour. After this, 1 rat unit was excreted every three minutes until the ninety-six hour, when the rate of excretion diminished. When the hormone was given in oil and wax or oil and cholesterol its appearance in the urine was delayed and was never in the amount as when aqueous solution was used. This was taken to mean that the release of the hormone from the injection site was slowed by using oil and wax or oil and cholesterol.

From the observations of others and because of their own postpartum studies, the authors believe that chorionic gonadotropin is filtered through the kidney slowly. Computing the amounts of gonadotropin recovered in the urine after injection indicated that there was relatively little destruction or utilization of the hormone in the body. Because of the slow excretion of the hormone by the kidney there was no advantage therapeutically in using an oily medium to delay absorption at the site of injection. C. J. Ehrenberg.

EXPERIENCES WITH Rh HAPTEN

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RECENTLY, a new approach to the treatment of erythroblastosis fetalis was suggested by Carter.[1-3] In 1941, Levine and his co-workers[4] had shown that the pathological state in the infant was due to antibodies elaborated by the mother during pregnancy. In more than 90 per cent of the cases, anti-Rh antibodies were the responsible agents.

It had previously been shown that, if a strong and a weaker antigen are injected concomitantly, antibodies are produced against the stronger antigen but not against the weaker one ("competition of antigens"). Wiener[5] has advocated the application of this concept to Rh sensitization and has immunized Rh-negative women with typhoid vaccine during pregnancy. Theoretically, by developing an immunity to the stronger antigen (typhoid), Rh (the weaker antigen) immunization should be suppressed. In practice, however, the desired results have not been achieved.

Lack of specific therapy has led to the development of the various forms of transfusions (small repeated or massive replacement transfusions) for handling the afflicted infants. Unfortunately, such treatment is of no avail for the stillborn children and many of the severely affected are born dead.

After more than two years of research, Carter[1] reported the isolation of a protein-free Rh hapten in 1946. A hapten, as originally defined by Landsteiner,[6] is a specific protein-free substance which, although active in vitro, induces no or only slight antibody response. Activity in vitro is manifest by the neutralization of specific antibodies produced against the complete antigen. Such activity has also been shown to occur in vivo. Others, notably Calvin and his associates[7] and Witebsky,[8] had previously isolated "Rh hapten substances" but not in the protein-free state. In 1948, together with Loughrey, Carter[2] successfully applied Rh hapten in the treatment of an infant severely affected with erythroblastosis fetalis. Since the publication of this case, she has furnished material for the treatment of fifty more infants and also has further extended the therapy to women who had previously delivered erythroblastotic infants.[3]

Using a slight modification of Carter's amended technique which has been published elsewhere,[3] Rh hapten has been produced in our laboratories and administered to several patients. The modification consisted of adding ultraviolet irradiation of the final product to eliminate any viruses present. A report of our initial results is given below. These are consecutive cases and are not selected ones.

Case Reports

CASE 1.—Mrs. R. Z., 29 years old, white, has been married six years. Her first pregnancy in 1944 resulted in a normal male infant after an uneventful antenatal course and

spontaneous, uncomplicated delivery. Her second pregnancy in 1946 was also entirely without incident and after a short labor and spontaneous delivery, a second male child was born but this infant had severe icterus gravis and anemia. Unfortunately, Rh antibody studies were not done during this pregnancy. The affected infant was treated with multiple (six) small transfusions and supportive therapy and after three weeks was discharged as cured.

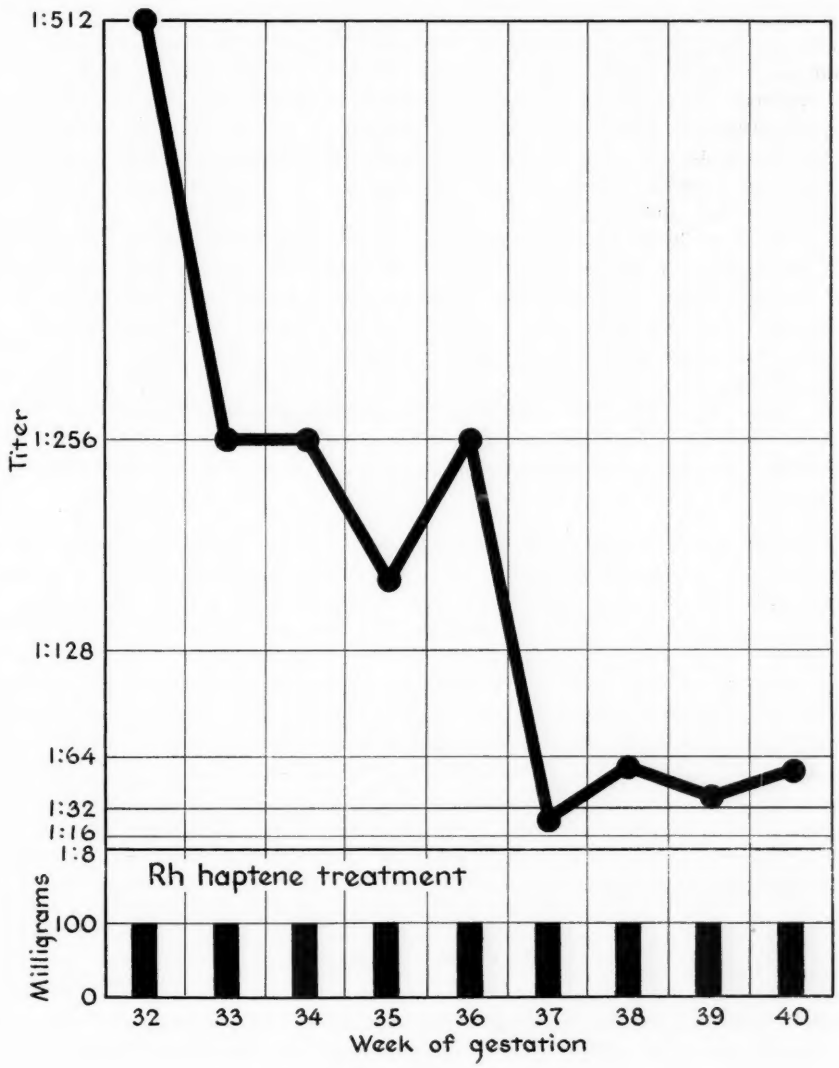

Fig. 1.—Maternal antititers, Case 1.

She again became pregnant in September, 1947, but was not seen until the third month of her pregnancy. At that time, a complete blood study of the mother and the remainder of the family was done:

BLOOD OF	GROUP	Rh TYPE	REMARKS
Mother	O	Rh neg.	
Father	O	Rh_1	Heterozygous
Daniel (4 years old)	O	Rh_1	Heterozygous
Robert (2 years old)	O	Rh_1	Heterozygous

Rh antibodies were first found in the maternal serum in January, 1948, at which time "blocking antibodies" in a titer of 1:28 were discovered. One month later, the titer had increased to 1:56 and remained at this level during March. At that time, through the courtesy of Mrs. Carter, Rh hapten was made available to us to treat this patient and after an initial lag period of one week, the titer fell progressively with treatment (Fig. 1) until on May 5, 1948, no Rh antibodies could be found. Treatment was continued at weekly intervals. Her expected date of confinement was June 17, 1948. However, on June 2, blocking antibodies were again found in the maternal serum in a titer of 1:8. A large dose of Rh hapten (300 mg.) was given and three days later, labor was induced. Blood taken on the morning of induction contained blocking antibodies in a titer of 1:2. Induction resulted in a three-hour labor and an 8 pound, 4 ounce male infant was then spontaneously delivered. The infant was normal in every respect. No edema or jaundice was present. The placenta was grossly normal and weighed 600 grams. The amniotic fluid was clear and colorless. Immediate blood study disclosed that the child was Rh positive (Group O; Rh_1, heterozygous). The red cell count was 6.04 million and the hemoglobin 16 grams. Only one nucleated red cell per 100 white blood cells could be found. Serum from cord blood contained no free Rh antibodies but the erythrocytes gave a weakly positive Coombs' test. The child was observed very closely during the next ten days but at no time during this period did the hemoglobin fall below 16 Gm. nor the red blood cell count below 6 million. On discharge from the hospital on the sixth day of life, the hemoglobin was 16.2 Gm. and the red blood cells 6.03 million. Since that time, the child has been seen frequently and at three months of age showed no abnormalities. He has maintained his hemoglobin and red blood cell count and has gained adequately.

CASE 2.—Mrs. H. S., 30 years old, white, was married seven years. She had an early (two to two and one-half month), spontaneous abortion in 1942 and did not again become pregnant until 1946. During this second pregnancy, it was discovered that she was Rh negative and Rh antibody determinations were made at frequent intervals. At thirty-two weeks, no antibodies were present but at the thirty-sixth week blocking antibodies in a titer of 1:10 were found in the maternal serum. Within one week, this titer rose to 1:5120 and several days later, the mother reported that she could no longer feel fetal movements. The fetal heart which had previously been heard easily was no longer audible. Ten days after this, Mrs. S. spontaneously delivered a macerated stillborn infant. Autopsy evidence of erythroblastosis fetalis was present, particularly in the enlarged liver and spleen in spite of the maceration. She again became pregnant in November, 1947. Her expected date of confinement was August 8, 1948. On her first prenatal visit in her third month, a complete study of the maternal blood and blood from her husband was done. The results were:

BLOOD OF	GROUP	Rh TYPE	REMARKS
Mrs. S.	A	Rh neg.	
Mr. S.	B	Rh_1	Homozygous

Thereafter, although the maternal serum was studied at frequent intervals, no Rh antibodies were found until March 16, 1948 (approximately twenty-two weeks of gestation) when blocking antibodies in a titer of 1:4 were found. When the serum was rechecked after two weeks, the same titer was found. Treatment with Rh haptene was therefore begun on April 18, 1948, at twenty-six weeks of gestation and continued at weekly intervals. The dosage was 100 mg. per week. The maternal serum was studied every week but no Rh antibodies were found after beginning the haptene therapy. Due to her previous history, it was decided to deliver this patient by cesarean section and on July 27, 1948, a living, female infant was so delivered. Although the amniotic fluid was light yellow in color, the child was normal in every respect and weighed 7 pounds, 6 ounces. No edema or jaundice was discernible. The placenta weighed 625 grams and showed no abnormalities. Blood studies on the infant immediately after birth showed her to belong to Group B, and she was Rh positive (Rh_1, heterozygous). The hemoglobin was 15.2 Gm. and the red blood cells numbered 4.86 million per cubic millimeter. There were four nucleated red cells per 100 white blood cells

in a smear of the peripheral blood. The Coombs' test on the cord blood was negative. Very close observation of this child was maintained for ten days. During this time, her hemoglobin maintained itself at or above 15.5 Gm. and the red blood cell count above 4 million without further therapy. The nucleated red cells disappeared from the peripheral blood within 24 hours. At the time of discharge from the hospital, the hemoglobin was 15.8 Gm. and the red blood cell count 5.13 million. Since that time, periodic observation has been continued. Her hemoglobin and red cell count have been maintained and she is progressing normally.

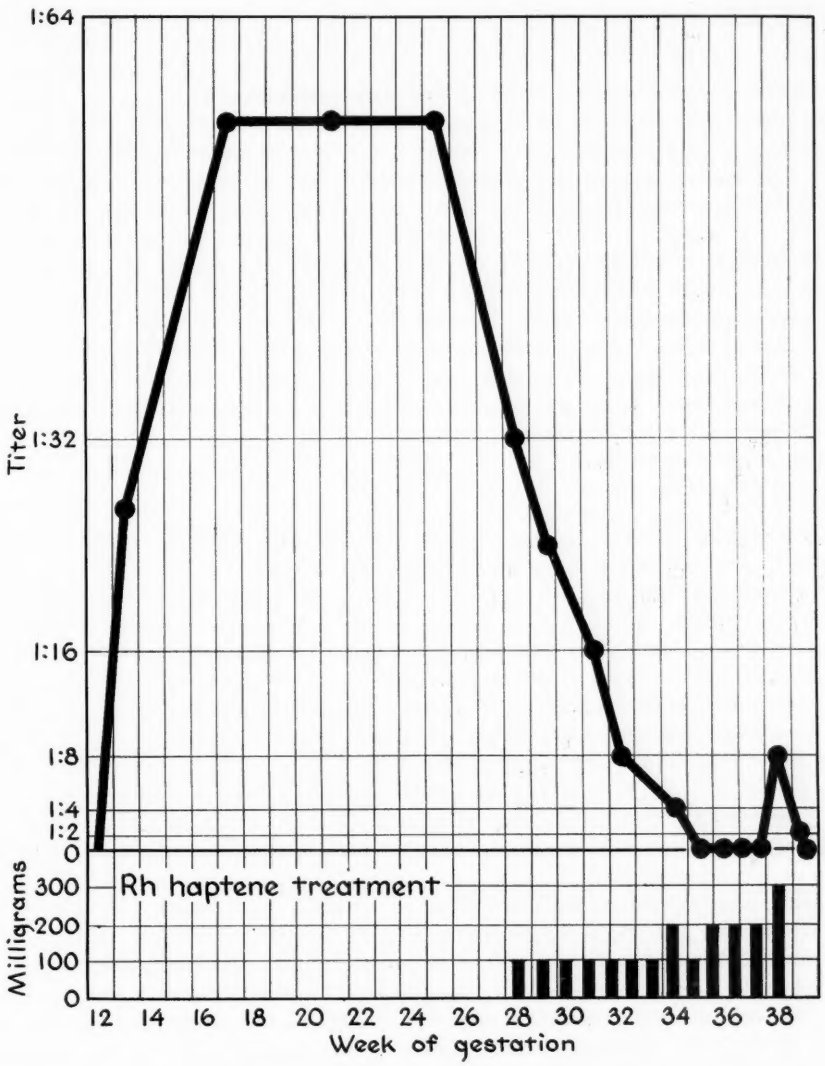

Fig. 2.—Maternal antititers, Case 3.

CASE 3.—Mrs. J. L., 35 years old, white, has been married thirteen years. In 1936, she had spontaneously delivered a normal, healthy male infant. Two succeeding pregnancies in 1938 and 1939 also resulted in normal, healthy male infants. Her fourth pregnancy, in 1944, was complicated by the intrauterine death of the fetus near term. An autopsy revealed evidences of erythroblastosis fetalis and at that time it was first discovered that the mother was Rh negative although no determination of Rh antibodies was made. She again

became pregnant in December, 1947. Her expected date of delivery was Sept. 20, 1948. Only one antibody determination was made in May (at about twenty-four weeks of gestation) at which time blocking antibodies in a titer of 1:32 were found. She was first seen by me in August, 1948, at approximately thirty-two weeks of pregnancy and a complete blood study of the patient and the remainder of the family disclosed:

BLOOD OF	GROUP	Rh TYPE	REMARKS
Mother	O	Rh Neg.	
Father	O	Rh_1	Heterozygous
Dennis (12 years old)	O	Rh_1	Heterozygous
Patrick (10 years old)	O	Rh_1	Heterozygous
Michael (9 years old)	O	Rh Neg.	

Blocking antibodies in a titer of 1:512 were present in the maternal serum. Treatment was begun and the curve of antibody titers together with the treatment intervals are given in Fig. 2. With treatment, the titer fell to 1:28 only to rise slightly thereafter. On Sept. 24. 1948, the patient began spontaneous labor and after eight hours delivered an 8 pound, 9½ ounce, severly jaundiced, markedly edematous infant. The liver and spleen were both markedly enlarged (to the level of the umbilicus). There were numerous petechiae and ecchymotic patches on both cheeks and over the sacrum. Immediate blood studies showed a hemoglobin of 8 Gm. and a red blood cell count of 2.52 million. There were 480 nucleated red cells per 100 white blood cells in a smear of peripheral blood. The baby was Group O and Rh positive. A markedly positive Coombs' test was obtained on cord blood. The placenta was large, edematous, and weighed 2½ pounds. Despite supportive therapy, the baby expired after one hour. Blood could not be obtained which was compatible for transfusion. A study of the maternal blood taken during labor showed blocking antibodies in a titer of 1:56 and agglutinating antibodies in a titer of 1:14. The diagnosis of erythroblastosis fetalis was confirmed by autopsy.

CASE 4.—Baby girl W. was spontaneously delivered after an easy four-hour labor. Mrs. W. had had three children previously all of whom were born alive and were normal. Although this child appeared normal at birth, within four hours she appeared to be slightly edematous and slightly jaundiced. At the end of eight hours the edema had increased considerably and the jaundice was pronounced. At that time it was first noted that the liver was enlarged to the level of the umbilicus and the spleen was palpable 3 cm. below the left costal margin. The hemoglobin was 8.5 Gm. and the red blood cell count 2.64 million per cubic millimeter. A positive Coombs' test was obtained on her blood and there were 550 nucleated red blood cells per 100 white blood cells in a smear of peripheral blood. The icterus index was 120. The baby was then given 75 c.c. of Group O, Rh-negative blood and 100 mg. of Rh hapten intramuscularly. The hapten (100 mg.) was repeated at the end of twelve hours. At that time, the hemoglobin was 10.5 Gm. and the number of nucleated red cells per 100 white blood cells had decreased to 300. Twenty-four hours later, a third injection of 100 mg. of Rh hapten was given intramuscularly into the buttocks. Hemoglobin was 11.5 Gm. and there were 100 nucleated red cells per 100 white blood cells on smear. At the end of sixty hours after delivery, the liver could be felt only 1 cm. below the costal margin and the spleen could no longer be palpated. The hemoglobin was 11.8 Gm. and only two or three nucleated red cells were found per 100 white blood cells in the smears. The edema had completely subsided and the jaundice was much less marked. After another twelve hours (three days after birth), all objective evidence, except slight jaundice, of erythroblastosis fetalis had disappeared. Thereafter, the child maintained her hemoglobin at or above 11.8 Gm. and the red blood cell count at or above 4 million. She was discharged from the hospital after two weeks as cured and although she has been seen frequently since her release has progressed and developed normally.

Discussion

Under most circumstances, it was to be expected that all three children mentioned in Cases 1, 2, and 3 either would be stillborn or would be severely affected with erythroblastosis fetalis at birth. Nevertheless, after treatment

with Rh hapten during pregnancy, two of the mothers delivered normal healthy children who were Rh positive.

As Carter has previously observed,[3] the difference between success (Cases 1 and 2) and failure (Case 3) apparently is a function of the time at which treatment is begun. It is believed that the Rh antibodies traverse the placenta after the seventh month of gestation. In order to prevent fetal damage which these antibodies produce, they must be rendered ineffectual before that time. Although there is no direct evidence as yet, it seems that the mode of action of Rh hapten is a neutralization or inactivation of the antibodies themselves since the hapten apparently will not affect a change in fetal damage which has occurred prior to its administration.

Rh hapten is a lipid which contains less than 2 per cent of nitrogen and is nonantigenic alone. In repeated tests both in animals and human beings, it has proved to be innocuous. No reactions, either local or systemic, have been encountered during prolonged use of saline suspensions of the material except for occasional instances of local soreness lasting from one to three days following the initial two or three injections.

In selected cases, erythroblastotic infants may also be treated with Rh hapten. In these instances, results have been more rapid and more dramatic than with the use of transfusions alone or with other supportive therapy. Apparently large doses given at frequent intervals (every eight to twelve hours) are essential and should be given as soon after birth as possible.

Obviously, no conclusions can be drawn from such a small series of cases. Many hundreds will be necessary before a critical evaluation can be made. Dosage and treatment intervals must be more carefully studied. Arbitrarily, injections have usually been given at weekly intervals and the size of the dose has been governed by antibody titer in the maternal blood. It is apparent from our own results and those previously reported by Carter and her associates[2, 3] that Rh hapten is not a cure-all but treatment with this material seems to have considerable promise as an addition to the therapy of erythroblastosis fetalis.

Summary

1. The case histories of three patients treated with Rh hapten during pregnancy and of one erythroblastotic baby treated after birth are reported.

2. Two of the mothers gave birth to normal, healthy children while the third, in whom treatment was begun during the ninth lunar month, produced an infant which was severely affected with erythroblastosis fetalis and failed to survive.

3. After three days, the baby treated after birth with Rh hapten was apparently cured and only slight jaundice remained thereafter.

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MORTALITY FOLLOWING EXCHANGE TRANSFUSION IN ERYTHROBLASTOSIS FETALIS

Preliminary Report

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EXCHANGE transfusion is now an accepted method of treatment of erythroblastosis fetalis and to date we have treated seventy-four erythroblastotic infants in this way. Our series of cases is now large enough to permit statistical analysis, and such an analysis has been carried out with the view of determining, if possible, ways of further improving the results of treatment. The purpose of this report is to point out one factor in the handling of the cases which appears to have a pronounced effect on the mortality rate in the disease.

In Table I are summarized our mortality statistics. The cases have been classified according to: (1) whether they had been diagnosed before birth with the aid of antenatal Rh-Hr tests and antibody studies, and (2) whether they were not recognized until after birth when jaundice and/or anemia became evident in the infant. The cases are further classified according to the method of delivery.

The over-all mortality was 16.2 per cent. Contrary to expectations, the mortality rate in the "neglected" cases, i.e., those not diagnosed until after birth, was considerably lower than in the cases diagnosed antenatally and treated promptly after birth. The explanation for this apparent paradox is that the latter group includes the most severe cases, namely, those in which there had been previous neonatal deaths and stillbirths from erythroblastosis. In the majority of these cases the infant had been delivered before term in order to reduce the period of exposure to the maternal antibodies and with the idea that the infant would be treated by immediate exchange transfusion after birth.

TABLE I. MORTALITY RATE AFTER EXCHANGE TRANSFUSION IN ERYTHROBLASTOSIS FETALIS

	TYPE OF DELIVERY	NUMBER OF CASES*	DIED	
			NUMBER	PER CENT
Diagnosed serologically *before* birth	(a) Cesarean section	15	7	46.6
	(b) Medical induction	23	2	8.6
	(c) Spontaneous	13	2†	15.3
	Totals	51	11	21.9
Diagnosed clinically and serologically *after* birth	Spontaneous	23	1	4.3
Totals		74	12	16.2

*This includes all cases treated by us to date including those previously reported, except one case which we were called upon to treat on the fourth day when the infant was already moribund.

†In one of these two cases the infant was premature; in the second the baby died at the age of 30 days with pyemia.

When the cases diagnosed antenatally are further classified according to the method of delivery, the interesting fact comes to light that the majority of the fatalities occurred in those infants delivered by cesarean section. In the infants delivered following induction of labor, the mortality rate was less than one-fifth as high even though the infants were in comparable states of prematurity and the severity of the disease was approximately the same, as judged especially by the maternal antibody titers at the time of delivery.

Based on these data it would seem that the method of delivery of the erythroblastotic infant has a pronounced effect on the mortality rate. Our patients who were delivered by cesarean section could very well have been delivered by medical induction instead. It seems fair to conclude, therefore, that if cesarean section is avoided as a method of delivery of erythroblastotic babies a substantial reduction in mortality rate will result. In our own series of cases, if we had excluded those delivered in this manner, the mortality rate would have been less than 10 per cent.

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Govan, A. D. T., and Scott, Jean M.: Intravenous Use of Iron in Treatment of Anemia of Pregnancy, Lancet, p. 14, Jan. 1, 1949.

Intravenous administration of saccharated iron oxide has been shown to be safe and nontoxic, and free from the danger of hemochromatosis. For the rapid relief of anemia in pregnancy, the authors used doses of Ferrivenin equivalent to 30 mg. of elemental iron on the first day, 60 mg. on the second, and 100 mg. daily thereafter. At the end of a week injections are reduced to 100 mg. every other day. In twenty-five anemic pregnant women so treated there was rapid relief of symptoms. There was an average hemoglobin rise of 8 per cent (0.9 Gm. per 100 c.c.) after one week of treatment. The initial reticulocyte and hemoglobin responses were greater in more severely anemic patients. As treatment continued, the weekly hemoglobin increment improved, in contrast with the diminishing effect of oral iron in patients with disappearing anemias.

The authors recommend this mode of iron therapy in (a) latent anemias becoming clinically apparent late in pregnancy, where time is a factor, (b) intolerance of iron by mouth (30 per cent of pregnant women), (c) iron-refractory anemias of pregnancy.

Irving L. Frank.

McElin, Thomas W., and Lovelady, Sim B.: Choreiform Behavior During Pregnancy With Data on Five Cases, Proc. Staff Meet. Mayo Clin. **23**: 382, 1948.

Five cases of chorea gravidarum have been treated at the Mayo Clinic; the average age of the patients was 21 years; three were multigravidas and two primigravidas. In all cases the chorea began in the first half of pregnancy; the duration of the symptoms varied from two and one-half weeks to five months. In all cases delivery was spontaneous at term, and the infants were normal (one pair of twins). In all cases there was a definite history of rheumatic fever or active rheumatic fever, and rheumatic heart disease in three cases. There was no evidence that toxemia was an etiologic factor. "Pyschogenic color," as described by Weigner in his article in 1937, was a factor in four cases.

Harvey B. Matthews.

AN ANALYSIS OF BREECH DELIVERIES IN A GENERAL HOSPITAL*

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BREECH presentation must be rated as a pathologic delivery. The necessity for deep surgical anesthesia, the presence of a skilled assistant, and the possible eventuality of forceps application are only three factors which increase the seriousness of the problem. In addition the fetal and maternal mortality are increased to such an extent even in the hands of an expert that the assumption of a normal outcome is unjustified. The high incidence of puerperal sepsis subsequent to increased trauma adds even more to the hazards. In spite of extensive experience with the problems of extraction of arms and the aftercoming head following internal podalic version, Potter[1] considers breech presentation one of the most serious complications of labor. Many others consider the management of breech delivery an index of the physician's obstetrical judgment and ability.

A review of the recent literature reveals the concern of obstetricians over the hazards to both mother and child during breech delivery.

Table I lists data from the maternity services of five large teaching hospitals and one general hospital. We must recognize the fact that in institutions devoted entirely to obstetrics the facilities for the care of the parturient can be maintained on a slightly higher level than is possible or practical in a general hospital. However, the statistics are illustrative of the variations and magnitude of the fetal mortality even when corrected by deleting premature births, nonviable infants, serious congenital anomalies, and neonatal deaths not directly attributable to the delivery.

Table I. Fetal Mortality in Breech Presentations

Hospital	Author	Year	Fetal Mortality	
			Gross (per cent)	Corrected (per cent)
University Hospital, Baltimore	Siegel and McNally[2]	1939	28.1	12.1
Margaret Hague Hospital	Waters[3]	1942	11.2	
Sloane Hospital	Watson[4]	1943	5.3	
Philadelphia Lying-In	Tompkins[5]	1943	10.4	2.7
Chicago Lying-in	Dieckmann[6]	1945	3.8	1.7
Millard Fillmore Hospital	Potter[1]	1944	17.4	9.6

Table II demonstrates the fact that breech delivery adds to the hazards of labor for the mother since both the mortality and morbidity are increased at least threefold over the accepted standards for all presentations.

*Presented at the regular meeting of the Pittsburgh Obstetrical and Gynecological Society, Oct. 11, 1948.

TABLE II. MATERNAL MORTALITY AND MORBIDITY IN BREECH DELIVERIES

HOSPITAL	AUTHOR	YEAR	MATERNAL MORTALITY (CORRECTED) (PER CENT)	MATERNAL MORBIDITY (PER CENT)
Hospitals of Brooklyn, New York	Gordon et al.	1926-30	.49	
Millard Fillmore Hospital	Potter et al.	1944[1]	.89	11.5

Accepted standards for maternal mortality and morbidity in all presentations are 0.19 per cent and 3.5 to 4 per cent, respectively.

The foregoing facts outline the problems of breech presentation as found in other hospitals and the purpose of this investigation was to determine the conditions that existed in our own general hospital and make comparison.

All deliveries occurring from Jan. 1, 1930, to Dec. 31, 1947, on the Obstetrical Service of the Pittsburgh Hospital were reviewed. The chart of each patient with a primary breech presentation was studied. The history and labor records were compared to confirm age, parity, and duration of gestation. Pregnancy of thirty-eight weeks or more was considered as full-term gestation. The duration and complications of labor were recorded together with the condition of the child at birth. The clinical sheet was examined for evidence of febrile reaction during the puerperium. A temperature of 100.4° F. occurring on two days of the postpartum period exclusive of the first twenty-four hours was considered morbid. The fate of the infant in the neonatal period was recorded as its condition upon discharge.

Results

Fetal Aspect.—

During the period mentioned above there were 13,506 consecutive deliveries, and primary breech presentation occurred 506 times, or an incidence of 3.7 per cent. There were two cesarean sections elected for the presentation alone and the fetal mortality for delivery was computed upon the remainder. The gross fetal mortality for all presentations is shown in Table III.

TABLE III. FETAL MORTALITY IN BREECH DELIVERY

	NO. OF CASES	STILLBIRTHS AND NEONATAL DEATHS	TOTAL NO. OF CASES	TOTAL STILLBIRTHS AND NEONATAL DEATHS	FETAL MORTALITY (PER CENT)
			504	91	18.0
Nonviable fetus	17	17			
Remainder			487	74	15.1
Premature	52	16			
Remainder			435	58	13.3
Congenital defects	12	12			
Remainder			423	46	10.8
Maceration of fetus	6	6			
Remainder			417	40	9.5
Abruptio placentae	4	4			
Remainder			413	36	8.7
Toxemias of pregnancy	3	3			
Remainder			410	33	7.5
Placenta previa (marginal)	2	2			
Remainder			408	31	7.5
Hydrops fetalis	1	1			
Remainder			407	30	7.3
Gross fetal mortality in all presentations					5
Gross fetal mortality in breech presentations					18

Among the fetal complications not recorded in the table are seven cases of prolapsed cord, or an incidence of 1.3 per cent. In none of these was there a fetal death directly attributable to this hazard. In addition there were four recorded cases of injury to the upper extremities including three paralyses of the brachial plexus and one fracture of the humerus.

Maternal Aspect.—

The outcome in breech delivery as concerns the mother is also of grave concern. The duration of labor in primiparas was found to average 15 hours, 20 minutes, while in multiparas it was 11 hours, 20 minutes. The maternal morbidity for the seventeen-year period was 10.2 per cent and the mortality for the same time was 0.78 per cent. Three of the five maternal deaths subsequent to breech delivery were due to puerperal sepsis and two were attributed to postpartum hemorrhage. Additional trauma to the mother included one case of rupture of the lower uterine segment and a high incidence of cervical lacerations and extensive perineal tears.

TABLE IV. MATERNAL MORTALITY AND MORBIDITY

		MORBIDITY	MORTALITY
All presentations	1930-1947	(See below)	.21%
Breech presentations	1930-1947	10.2%	.78%

Accepted average maternal morbidity for all presentations is 3.5-4.0%

Discussion of Results.—

The data derived from this study are not significantly different from the findings of other investigators, as is shown in Tables I and V.

TABLE V. INCIDENCE OF BREECH PRESENTATION (TOMPKINS)

	PERCENTAGE	NO. OF DELIVERIES
Moore and Steptoe	2.8	51,571
Danforth and Galloway	3.3	8,531
Cannell and Dodek	3.4	16,166
Morton	3.5	8,509
Waters	4.3	20,000
Walsh and Kuder	4.7	29,683
Patton and Mussey	4.8	6,195

One fact, perhaps not generally appreciated, is that the duration of labor in breech presentation is actually shorter on the average than vertex presentations. Textbooks call attention to the fact that labor is frequently prolonged. This is attributed to the inability of the soft breech to engage the lower uterine segment as well as the firm vertex. Cannell and Dodek[7] in 1934 found that labor in breech delivery was actually shorter than in vertex. Their findings were 15 hours and 12 hours for primiparas and multiparas, respectively.

This decreased duration of labor is probably accountable to the shortening of the second stage.

TABLE VI. DURATION OF LABOR

	PRIMIPARAS (HOURS)	MULTIPARAS (HOURS)
Vertex presentations (average)	18	12
Breech presentations (Cannell and Dodek)	15	12
Breech presentations (Gibson)	$15\frac{1}{3}$	$11\frac{1}{3}$

Since breech presentation can have in a high percentage of cases such a tragic outcome for both mother and child, it behooves us to attempt to im-

prove the chances for a successful termination. Modern obstetrics should provide the patient with the best chance of survival and the assurance that she will remain in good health and at the same time have a normal healthy infant.

The advantages of external cephalic version are obvious for a potentially dangerous presentation is converted into one in which the prognosis is markedly improved. The disadvantage of such version is the risk of placental separation, of fetal asphyxia, and of creating an abnormal presentation. In addition, it is often a most difficult procedure especially in frank breech presentations where the flexed thighs and extended knees splint the fetal body. Even those who advocate prophylactic version warn against attempting it in such cases. Unfortunately, the correct diagnosis of the presentation is often not made until the membranes have ruptured and labor has advanced to a point where version is impossible. Therefore, this procedure is only a partial solution to the problem.

When breech delivery through the pelvis is necessary or elected, the pitfalls of such an abnormal mechanism and the consequences of it to mother and infant should be borne in mind. Such patients should have a careful re-examination and evaluation of age, parity, obstetrical history, pelvis, and an estimation of the fetal size by the Clifford or Ahlfeld methods. X-ray pelvimetry will be of inestimable aid. Labor should then be carefully supervised and dystocia promptly recognized. Routine breech extractions done at full dilatation of the cervix are probably not justified for such interference is almost certain to add to the already considerable maternal risk. However, if no progress occurs within an hour of full dilatation, preparation for delivery should be started. The patient should be under deep surgical anesthesia and all manipulations must be done with deliberation and ease. The episiotomy is important and an adequate one done early will aid in the delivery of the after-coming head and avoid many complete lacerations of the perineum. The Celsus-Wigand-Martin maneuver is preferable to the Mauriceau-Smellie-Veit. Forceps are never applied until the widest diameter of the head has passed the inlet. A last but very important point of technique is that of postpartum inspection of the cervix with adequate repair when necessary.

Conclusions

1. Pelvic delivery of the breech presentation enhances the risk of parturition to both mother and child.

2. Prophylactic external cephalic version, if feasible, should be repeatedly attempted during the last eight weeks of pregnancy.

3. Breech delivery through the pelvis necessitates a thorough reinvestigation of the patient, with cephalopelvic disproportion and possible dystocia foremost in mind.

4. The average duration of labor in breech presentation is shorter than in vertex presentations and abnormal labor should be promptly recognized.

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PROPHYLACTIC USE OF PENICILLIN AND STREPTOMYCIN IN CERTAIN OBSTETRIC CONDITIONS

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EVER since antibiotics have been available for routine usage, the prophylactic potentialities of substances capable of destroying the living agents of disease in vivo have received serious consideration. The possible prophylactic value of penicillin and streptomycin* in the prevention of puerperal infections, especially endometritis, after certain obstetrical conditions deserves investigation. This evaluation is worthy of attention because the practice of administering penicillin to febrile puerperal patients and also in cases of suspected contamination is becoming increasingly popular without bacteriologic knowledge of the individual patients. With this in mind, studies were undertaken to find the course of both treated and untreated patients in whom febrile courses were more likely to occur.

The fact that bacteria begin to invade the uterine cavity with or shortly after the onset of labor is shown by Douglas and Rhees.[1] Some of these microorganisms remain for a protracted period, up to the forty-fifth postpartum day according to Hesseltine and Hite.[15] Today one rarely finds in a good maternity hospital a predominant strain such as *Clostridium welchii* or *beta hemolytic streptococcus,* although in the day of poor asepsis endometritis was commonly due to the latter organism. Hite, Hesseltine, and Goldstein,[2] and Hite and Hesseltine[3] have shown that by present-day bacteriologic techniques, cultures are not significant as a rule in determining the causative organism in puerperal endometritis. An exception may exist when there is a predominant strain; otherwise it is only problematical which organism is the invader. The role of synergistic and antagonistic action of bacteria in the puerpera is not fully understood nor appreciated. Hite and Hesseltine[4] have demonstrated the synergistic relationship with some of the common vaginal and puerperal intrauterine bacteria. The final clinical appraisal of the prophylactic application of antibiotics must necessarily be one of speculation for one cannot be sure bacterial infection would or would not have occurred. At the same time, if the postulate of prophylaxis be made, effective concentrations of the drugs used must be maintained over a sufficient period of time to prevent invasion in the host animal.

Power and Cravotta[5] have recommended the use of penicillin for many obstetrical conditions. These include acute mastitis, septic abortions, pyelitis due to streptococcal infections, postpartum pelvic cellulitis, newborn omphalitis, routinely for cesarean section, and prophylactically for prolonged ruptured membranes, uterine inertia, and long labors. Our study was concentrated on those patients subjected to long labor, Dührssen's incisions, intrauterine pack and exploration, intrapartum infection, and perhaps other conditions in which the chance of a febrile puerperal course was more likely. Septic abortions come rarely to this institution.

*Generous supplies of penicillin and streptomycin for this research were donated by Merck & Co., Inc.

Clinical Studies

Our criteria for use of an antibiotic were: (1) any patient who had been in active labor for twenty-four hours and was not imminently likely to deliver, (2) any patient subjected to Dührssen's incisions or treated by an intrauterine pack, (3) any patient developing an intrapartum febrile course, and (4) a few other conditions in which febrile puerperal courses were more likely. Appropriate laboratory tests, and intrauterine and blood cultures were employed for evaluation when indicated. If the patient developed a febrile course after delivery but before the lapse of the first forty-eight-hour period, the antibiotic was continued until the patient improved or until it could be assumed the antibiotic was ineffectual. Penicillin could be used for several days while streptomycin was not used over four days after delivery whether there was failure or improvement because of concern that certain bacteria might become resistant to streptomycin.

Four groups of patients were studied. One group received 20,000 units of penicillin intramuscularly every three hours, 160,000 units daily, until forty-eight hours after delivery, or longer when febrile. This group included fifty-one patients (thirteen multiparas; thirty-eight primiparas) who were studied during 1945 and the early part of 1946.

The second group of sixty-five patients (fifteen multiparas; fifty primiparas) who delivered from 1943 to 1945, and presented the same type of obstetrical conditions, in whom no prophylactic therapy was instituted, constituted a control group.

The third group of sixty-seven patients, chosen for a comparable period in 1934-1935 (thirteen multiparas; fifty-four primiparas), had received no prophylactic therapy.

The fourth group received 300,000 units or 0.3 Gm. of streptomycin intramuscularly every three hours (2.4 Gm. daily) for at least forty-eight hours after delivery. If the patient became febrile, streptomycin was given for an additional twenty-four hours and then discontinued. This group included forty-two patients (twelve multiparas; thirty primiparas) who were studied during 1947 and the early part of 1948.

TABLE I. PENICILLIN FOR PROPHYLACTIC VALUE IN CERTAIN OBSTETRIC COMPLICATIONS, 1945-1946

		POST PARTUM		
		AFEBRILE	FEBRILE	TOTAL
Prolonged labor		10	1	11
Prolonged ruptured membranes		11	1	12
Dührssen's incisions		14	4	18
Intrauterine pack and exploration		5	2	7
Intrauterine bag		1	0	1
Intrapartum fever		1	1	2
Total		42	9 (17.7%)	51
Multiparas	13			
Primiparas	38			51
Average labor, 28 hours				
Fetal deaths:				
Stillborn	3			
Neonatal	3			6

In the group that received penicillin (Table I), nine (17.7 per cent) of the fifty-one were febrile post partum. There were six fetal deaths, three stillborn and three neonatal. In the control period 1943-1945, only ten of the sixty-five

patients had febrile postpartum courses (16.4 per cent) (Table II). There were two fetal deaths, one stillborn and one neonatal. In the 1934-1935 period, out of sixty-seven cases, twenty-three had febrile postpartum records (34.3 per cent) (Table III). There were ten fetal deaths, seven stillborn and three neonatal. In the last group (those on streptomycin) four of the forty-two patients had febrile postpartum courses (9.5 per cent) (Table IV). There were eight fetal deaths, seven stillborn and one neonatal. The standard use for morbidity is the regularly employed one of 100.4° F. on two successive days excluding the first postpartum day.

TABLE II. CONTROLS FOR PENICILLIN PROPHYLACTIC GROUP. NO PENICILLIN OR OTHER AGENT USED TO PREVENT INFECTION, 1943-1945

		POST PARTUM		
		AFEBRILE	FEBRILE	TOTAL
Prolonged labor		5	3	8
Dührssen's incisions		38	7	45
Intrauterine pack and exploration		12	0	12
Total		55	10 (16.4%)	65
Multiparas	15			
Primiparas	50			65
Average labor, 32 hrs. 25 min.				
Fetal deaths:				
Stillborn	1			
Neonatal	1			2

TABLE III. CONTROLS FOR PENICILLIN PROPHYLACTIC GROUP. NO PENICILLIN OR OTHER AGENT USED TO PREVENT INFECTION, 1934-1935

		POST PARTUM		
		AFEBRILE	FEBRILE	TOTAL
Prolonged labor		2	0	2
Dührssen's incisions		32	16	48
Intrauterine pack and exploration		8	4	12
Intrauterine bag		2	1	3
Intrapartum fever		0	2	2
Total		44	23 (34.3%)	67
Multiparas	13			
Primiparas	54			67
Average labor, 40 hrs. 42 min.				
Fetal deaths:				
Stillborn	7			
Neonatal	3			10

TABLE IV. STREPTOMYCIN FOR PROPHYLACTIC VALUE IN CERTAIN OBSTETRIC COMPLICATIONS, 1947-1948

		POST PARTUM		
		AFEBRILE	FEBRILE	TOTAL
Prolonged labor		10	2	12
Dührssen's incisions		12	0	12
Intrauterine pack and exploration		7	2	9
Intrauterine bag		1	0	1
Intrapartum fever		8	0	8
Total		38	4 (9.5%)	42
Multiparas	12			
Primiparas	30			42
Average labor, 19 hrs. 35 min.				
Fetal deaths:				
Stillborn (antepartum, 3)	7			
Neonatal	1			8

Prolonged labors included "long labors" which lasted more than twenty-four hours in which delivery was not imminent. Prolonged labor with a dead fetus was considered an additional hazard because a dead fetus offers a good medium for bacterial growth. Dührssen's incisions almost always had been preceded by long labors. The intrauterine packs were used in the treatment of postpartum hemorrhage and in many instances manual removal of the placenta was part of the treatment. Manual removal was performed for hemorrhage or incomplete separation. Anderson[6] a few years ago demonstrated that intrauterine packs could be left in for several days when impregnated with a sulfonamide. This seemed like a significant contribution but studies now underway suggest other factors may be present. An intrapartum fever was defined to include temperatures of 100.4° F. or over during the course of labor.

Discussion

A survey of these data revealed that those who received penicillin prophylactically did not have a lower morbidity rate than did the control group (a comparable number of like conditions not so treated immediately before the introduction of this study). By contrast, the morbidity rate in a similar group of a decade before was considerably higher, which may be explained in part by improved obstetrical management, better aseptic technique, and perhaps more significantly by the currently shorter labors, and improved postpartum care of the present-day obstetrics in all the good maternity services. Those patients on streptomycin presented the lowest morbidity rate. Yet this is the smallest group by number and the average length of labor was the shortest of all the groups. A larger series might change this result appreciably. Due to the dangers of strain resistance and complications of one kind or another by the antibiotics one cannot yet be certain that streptomycin should be used so freely.

It appears unquestionably certain that the use of antibiotics as a preventive measure will not be effective in all cases; nevertheless, antibiotics may have some prophylactic value in selected cases when febrile puerperal courses might be expected.

The dosage of penicillin and streptomycin was chosen arbitrarily and on the basis of acceptable amounts with reasonable safety. As a general rule, bacteria which are highly susceptible to a particular antibiotic require smaller doses than those which are only moderately susceptible. For this reason the identification of a specific causative organism would be of great value in determining the dosage and frequency of administration of the antibiotic. In this study such bacteriologic information was not practically or, in most instances, technically available. Some microorganisms could be effectively inhibited by 40,000 to 50,000 units of penicillin per twenty-four hours, while others would require 400,000 to 1,000,000 units or more. The amount of 200,000 units per twenty-four hours should represent an approximate average prophylaxis dose. In retrospect it would seem that this group should have received not less than 400,000 units and perhaps twice this amount per twenty-four hours. In the instance of streptomycin, it has been shown that the minimal adult daily dose is 2.0 to 3.0 Gm. (2,000,000 to 3,000,000 units) per twenty-four hours. The total twenty-four hour dosage of streptomycin was 2.4 Gm. (0.3 Gm. every three hours

intramuscularly). Approximate therapeutic dosage was deemed necessary because of the possibility of producing bacteria totally resistant to this agent. It is established some bacteria can develop total and perhaps permanent resistance.

A valuable feature of these two antibiotics is their relatively low toxicity for man. By comparison penicillin is superior to streptomycin in this respect. The kinds and degrees of untoward reactions may depend upon the purity of the material administered. Although rare, urticaria and dermatitis, possibly on an allergic basis, have been the most frequent untoward reactions following the use of penicillin produced by the best antibiotic producers. Therapeutic shock or Herxheimer reactions following the use of penicillin have been reported only in the presence of syphilis and in accordance with the therapeutic dosages. Leavitt[7] has reported that penicillin may stimulate uterine contractions and bleeding in pregnant women. However, abortion has not occurred as predicted by Leavitt. Streptomycin, like penicillin, has been responsible for headache, fever, peripheral vasodilatation (possibly due to histamine-like impurities), and skin rashes. However, streptomycin has presented a complication of toxicity, which in some instances is irreversible, by involvement of the auditory and/or labyrinth branches of the eighth nerve to the extent of causing deafness, tinnitus, and vertigo. The majority of patients developing these untoward effects received streptomycin over a period longer than a week. There were no eighth nerve symptoms in our group. Thus far no uterine contractions were observed following the use of streptomycin or penicillin. Both penicillin and streptomycin pass readily through the placental barrier into the fetal circulation. Greene and Hobby,[8] Herrell, Nichols, and Heilman,[9] Woltz and Zintel,[10] and others have shown that penicillin readily and promptly reaches the fetus from the intramuscular route. Davis and Hesseltine[11] have found that a reverse diffusion also is possible by instilling penicillin or streptomycin into the amniotic cavity and obtaining blood levels of the antibiotic in the mother and the cord blood. There were no untoward reactions by either of these drugs observed in this study to the mother or the unborn fetus.

The number of different bacteria which have been found in the postpartum uterine cavity raises the controversial question of antagonistic and synergistic relationship. Hence, the bacteriologic population may be greatly disturbed or altered by the administration of an antibiotic. The uterus may be invaded by cocci and bacilli, anaerobic and aerobic bacteria. Many of the organisms found within the postpartum uterine cavity are similar to the vaginal flora type. According to Hite, Hesseltine, and Goldstein,[2] the vagina is the expected source and is the principal route of endogenous infection. Many of these bacteria are completely or highly resistant to penicillin and streptomycin while others are equally susceptible (Hite and Hesseltine[4]). This is true also of many bacteria common to the intestinal tract and adds support to the idea that the vaginal flora results from factors in the vagina favoring bacterial balance somewhat similar to the balance maintained in the bowel. It must be admitted that antibiotics may have prophylactic value for some organisms but at the same time they may remove the antagonistic balance for other potential pathogens.

A further point of consideration in the prophylactic use of antibiotics is the capacity of bacteria to develop acquired resistance to the inhibiting chemical

agent. It has been well demonstrated by Miller and Bohnhoff[12] that many organisms develop penicillin resistances rapidly and that once this resistance has developed it may be impossible to use sufficient penicillin to affect the strain. Similar data[13] indicate that acquired resistance to streptomycin may develop even more rapidly, although the mechanism may be somewhat different from that of the resistance to penicillin. One may undoubtedly expect acquired resistance to result from inadequate or improper treatment.

The report of Douglas and Landesman[14] which showed that the combined use of sulfadiazine and penicillin had prophylactic value appeared as this report was prepared for submission for publication.

In conclusion, the use of penicillin and streptomycin as prophylactic agents under the conditions of this experiment has not proved its value for routine administration. Ideally one would like to isolate specific organisms in suspected contamination and determine the susceptibility of these organisms to the inhibitive action of a particular antibiotic. Unfortunately this is seldom possible and when it is, frequently it is difficult to determine a predominant invader. On the other hand, in particularly selected cases under close management antibiotics may have prophylactic value. Prophylaxis probably does not prevail as much as actual early therapy. According to present view, if one is to use penicillin its dosage should be at sufficiently regular intervals to insure adequate therapeutic blood levels. Once penicillin or streptomycin is started, it should be continued until the patient is safely afebrile or failure is evident. The routine use of streptomycin as a prophylaxis is not recommended even in view of these data because of possible eighth nerve injury and also the likely chance of producing strain resistant to streptomycin. Furthermore, patients who have been in long labor with ruptured membranes should not be subjected to serious obstetrical procedures with the expectation that antibiotics will reduce the hazards of puerperal infection. Contrary to some views the routine and indiscriminate use of antibiotics is not a recommended procedure. Under certain conditions penicillin may and should be used in long labor and in those conditions in which intrapartum infection may arise as protection to the unborn.

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THE ROLE OF INFECTION IN PREMATURE RUPTURE OF THE MEMBRANES

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AMONG the causes of infant mortality, premature birth has been found to rank high. Many of these premature births are brought about by premature rupture of the membranes. On this basis, a study was undertaken to determine the cause of premature rupture.

It seemed logical that an infectious process in the cervical canal might extend itself to the membranes overlying the internal os; these membranes, becoming inflamed and friable, might then give way under the duress of a strong Braxton Hicks contraction or other strain.

The literature was searched for a similar approach to this problem, but we were unable to find such reports.

Methods and Materials

All cases in this series were taken from the labor and delivery rooms of the Miami Valley Hospital, during a consecutive four-month period from January through April, 1948. Patients who evidenced prematurity were questioned and examined in order to determine the length of gestation and possible contributing causes of premature labor. A total of nine patients were selected initially, but two were rejected prior to study because of insufficient evidence of prematurity. Twelve full-term controls were selected at random and without regard to history, parity, etc.

In order to assure recovery after delivery of those portions of the membranes covering the internal os, a 1 per cent alcoholic solution of gentian violet was swabbed over these membranes during the first stage of labor. The technique depended somewhat upon the intactness or previous rupture of the membranes, and upon cervical dilatation. Following delivery of the placenta, the membranes were washed, and several sections of dye-stained tissue were cut away from the sac. These stained portions were invariably found on the rim of the torn area. The tissues were fixed in 10 per cent formalin, and serial sections made. Hematoxylin-eosin was the stain used.

Of the twelve controls, five were primigravidas and three were gravida ii. Pregnancies in the other four of this group numbered three, four, six, and seven, respectively. Birth weights of the infants in this group varied from 5 pounds, 13½ ounces to 8 pounds, 6 ounces, with an average weight of 6 pounds, 12 ounces. One set of twins was in this group.

Of the premature cases, three patients were gravida ii, and four patients were primigravidas. Birth weights of their infants varied from 1 pound, 14 ounces to 5 pounds, 4 ounces, with an average weight of 3 pounds, 12½ ounces. One set of twins was in this group. Pertinent historical data of both sets of patients will be given later in the discussion.

Results

Gross Findings.—In all except two of the control group, the membranes appeared as smooth, shiny tissues of pink-grey color. They were supple in consistency and cut with silky resistance. Of the two excepted cases, one showed a few scattered areas of nodular thickening, which seemed to be composed of hyalinized tissue; the other showed moderate thickening and dullness of appearance, with a few areas of gritty resistance to cutting.

In the premature group, in varying degrees but with no exception, the membranes were dull and even shaggy in appearance, rough and thick in consistency, and offered a gritty resistance to cutting. In some cases, old blood was found between layers of the membranes, as well as on the surface. In some instances, small papular lesions were noted on the membrane surfaces, diffusely scattered in some cases and conglomerate in others.

Microscopic Findings.—For comparison purposes, two sections of membranes from the control group are shown (Figs. 1 and 2). For practical purposes, these may be considered histologically normal, although it can be seen that the section shown in Fig. 2 is somewhat thicker than that in Fig. 1. The innermost (fetal) surface of the amnion is lined with a layer of cuboidal type epithelium, sometimes found pseudostratified. These cells rest upon a thin pink-staining base of singularly acellular tissue. Beneath this is a thicker layer of cellular connective tissue which contains many elastic fibers. This amniotic connective tissue is separated from similar type chorionic tissue by a thin layer of loose areolar fibers, which in many sections (Fig. 1) was found to be widely separated. This layer represents the fusion of the two original mesoderm layers. The chorionic epithelium is often ill-defined, and blends with the decidua in some areas (Fig. 2). The cells are darker in staining quality, and appear to be stratified. They also rest on a basement membrane that is acellular. The decidua, which is not seen in all sections, is usually thin, and composed predominantly of decidual and syncytial giant cells. Few to moderate numbers of leucocytes are present, confined in most instances to the deciduochorionic junction.

Representative photomicrographs are also shown of two of the seven premature cases. Sections not included, both of the control and the premature group, were similar in most basic respects to the ones shown. All photographs are approximately 100× magnification.

Control Group.—

No. 1. Gravida iii. Moderate connective tissue edema, mild to moderate lymphocytic infiltration at deciduochorionic junction. Occasional hyalinization of chorion.

No. 2. Gravida i. Moderate edema of connective tissue.

No. 3. Gravida i. Mild edema; essentially negative (Fig. 1).

No. 4. Gravida i. Similar to No. 3.

No. 5. Gravida vi. Mild but fairly diffuse lymphocytic infiltration. The chorionic epithelium appears to be autolyzed in some areas.

No. 6. Gravida vii. Decidua heavy and quite vascular; otherwise negative (Fig. 2).

Nos. 7 and 8. Gravida ii and iv, respectively. Similar to Fig. 1. Slightly more edema in No. 8.

Nos. 9 and 10. Gravida ii each. Moderate edema of connective tissues. In No. 9 there were also rare areas of hyalinization in chorion.

No. 11. Gravida i. Moderate edema. Mild lymphocytic infiltration near deciduochorionic junction.

No. 12. Gravida i. Similar to Fig. 1.

Premature Group.—

No. 1. Gravida i. Dense leucocytic infiltration; old and fresh blood; cellular degeneration. Some areas resemble early gangrene (Fig. 3).

No. 2. Gravida ii. One previous abortion at four months, cause undetermined. Fairly dense leucocytic infiltration, fibrosis, hyalinization, and some cellular degeneration. Some frank hemorrhage.

Fig. 1.

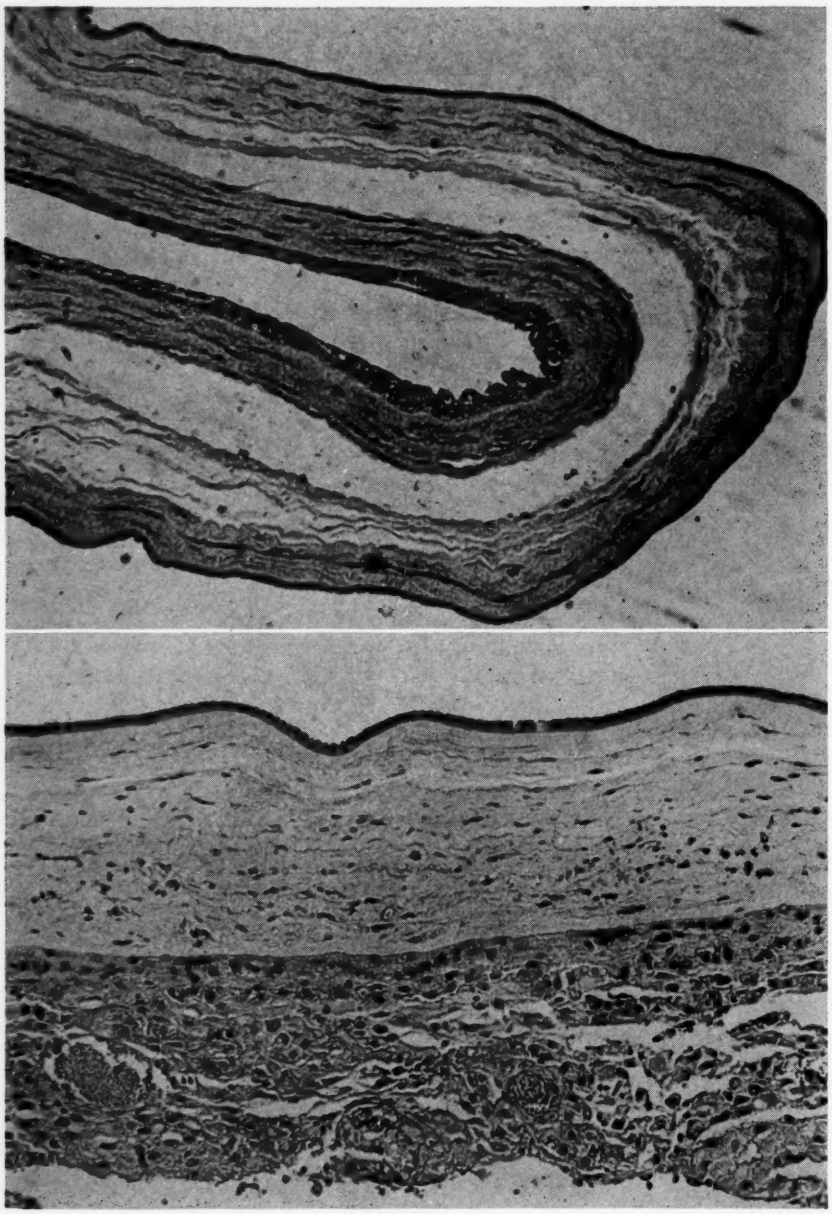

Fig. 2.

Fig. 1 (No. 3 Control).—Showing membranes in normal histological relationship.
Fig. 2 (No. 6 Control).—Normal membranes, somewhat thicker than in Fig. 1.

No. 3. Gravida i. Marked edema and hyalinization. Cellular vacuolization and degeneration. Several hyalinized nodules evident.

No. 4. Gravida iii. Extravasation of blood between amnion and chorion. Edema marked. Hyalinization and cell vacuolization throughout chorion. Previous full-term stillbirth, cause unknown.

No. 5. Gravida ii. Dense lymphocytic infiltration, vacuolization, hyalinization. Decidua is thick, with engorgement and cellular degeneration present.

Fig. 3.

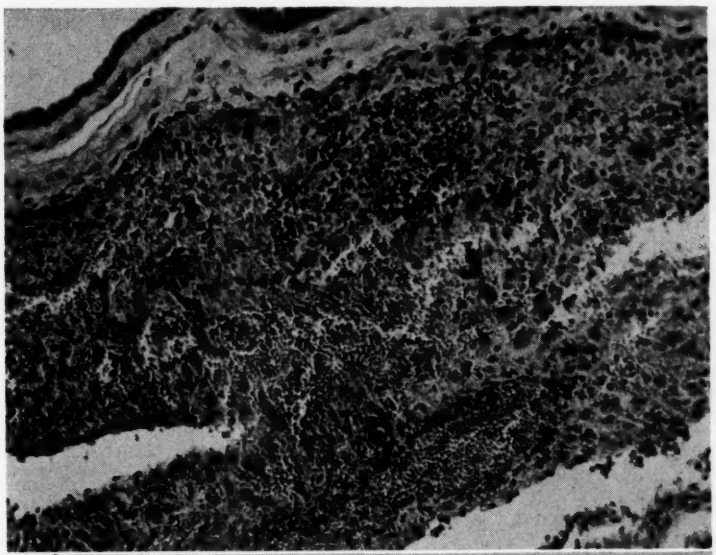

Fig. 4.

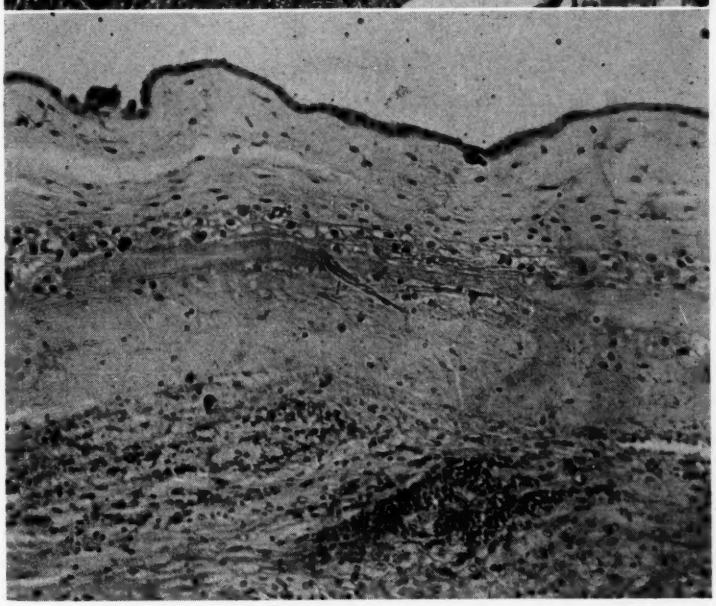

Fig. 3 (No. 1 Premature).—Marked inflammatory reaction is seen throughout entire section.

Fig. 4 (No. 6 Premature).—Diffuse hyalinization and leucocytic infiltration, with focal areas of neutrophilic infiltration.

No. 6. Gravida i (twins). Extensive hyalinization in chorion and decidua. Diffuse lymphocytic infiltration, with patchy areas of fairly dense neutrophilic infiltration. Some areas of necrosis found (Fig. 4).

No. 7. Gravida i. Marked hemorrhage and engorgement in chorion and decidua. Moderate to heavy leucocytic infiltration, mainly neutrophils. Degeneration and necrosis in many areas.

Discussion

As a whole, the membranes of the control group are comparable to normal. The edema and leucocytic infiltration seen in some sections are attributable to the trauma of labor and birth. We consider that in two of this group (Nos. 1 and 5) there is more than normal amount of reaction.

The membranes in all premature cases in this series show evidence of infection, acute or chronic or mixed. In most instances this reaction is severe.

It is certainly logical that membranes so infected are weakened, and that this weakening predisposes to premature rupture. In time, such infections may also produce changes in the uterus itself, resulting in an increased irritability of this organ. This factor, combined with ruptured membranes, makes expulsion of the fetus inevitable.

During the ten-year period of 1938 through 1947, a total of 20,512 births were recorded at the Miami Valley Hospital. Of these, 4.3 per cent were premature. The total uncorrected fetal mortality was 4.7 per cent. Of these total deaths, 22.7 per cent were premature infants. The mortality rate among premature infants alone was 23.5 per cent. In this series there were three deaths in eight premature births, a mortality rate of 37.5 per cent. These figures only bear out the well-known fact stated earlier in this paper, that prematurity is a leading cause of infant mortality.

Conclusions

Infection in the female reproductive tract (especially in the cervix) can cause premature rupture of the membranes and induce premature labor. This process is, in turn, responsible for many preventable infant deaths.

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TREATMENT OF GRANULOMA INGUINALE WITH STREPTOMYCIN

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UNTIL the discovery of streptomycin, the results of treatment of granuloma inguinale were routinely discouraging. Fortunately, within the past three years we have made rapid strides in the understanding and management of this disease.

Granuloma inguinale is endemic among people forced by their low economic standards to exist in crowded and unclean environments. It has a predilection for the Negro race almost to the point of suggesting an inherited susceptibility.[1] The epidemiology remains obscure and almost entirely unexplored. It has a low index of contagiousness, and although proof remains unconvincing, it is believed venereal in origin. Examination of marital partners of proved active cases rarely reveals the infection; promiscuity does not seem to play an active part in the spread of this disease.[3]

The first manifestation of granuloma inguinale is a slowly rising bubo in the groin, which eventually ruptures unfolding a bright red, velvety, granulation tissue. The early lesions are localized and clean; daughter lesions, however, soon develop and coalesce to cover the entire perineal and vulvar areas. A peculiarly pungent, fetid odor pervades the immediate vicinity of the afflicted person. Far-advanced lesions are incapacitating because of extreme pain and elephantoid swellings of the affected parts. Contamination with secondary invaders, chiefly fusospirochetes, adds to the loathsome picture. Extragenital lesions have been observed in the oral cavity and occasionally at the site of surgical wounds.[4]

Since 1905, when Donovan first discovered the well-defined parasites within certain tissue cells, little has been added to our knowledge of the causative organism.[5, 7] Attempts to grow Donovan bodies on various enriched media have failed; it has also been impossible to reproduce the disease in animals. In the human being, granuloma inguinale was reproduced in volunteers by injecting minute amounts of a pure suspension of Donovan bodies beneath the skin of the groin.[1] Recently, the organisms have been cultivated successfully in the yolk-sac of living chick embryos, thus opening new fields of investigation on the true nature of Donovan bodies.[6]

Treatment until recently remained obscure and almost entirely empirical. Antimonial compounds have been used with varying degrees of success in early lesions; however, in the later stages they are ineffectual as evidenced by one patient in our series whose treatment extended over a period of twenty years. The effectiveness of these drugs decreases in direct proportion to the chronicity of the disease.[2] Penicillin is entirely valueless as a specific agent but is paramount in the control of secondary invaders, thus allowing streptomycin to be more fully effective. Streptomycin has been used by numerous investigators in amounts ranging from 3.3 to 94 Gm. extending over varied periods of time.

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The results indicate that 20 Gm. of the drug given over a period of five days in divided doses are adequate.[2] Resistance of the Donovan body to streptomycin is prevented with this dosage.

Case Reports

During the past year we have successfully treated six patients afflicted with granuloma inguinale. All of the patients were Negroes and all but one were in their early twenties, married, with one or more offspring. Previous treatment ranged over a period of eighteen months to twenty years. In all patients the lesions were gruesome in appearance, foul smelling, and extremely painful. In every case specimens were taken for biopsy and Donovan bodies were located within tissue cells. Exudate from the lesions was examined for secondary invaders. In addition to granuloma inguinale two patients had syphilis and one, lymphogranuloma venereum. Tuberculosis and malignancy were excluded before the instigation of treatment.

Every patient received 1 Gm. of streptomycin in 5 c.c. of saline intramuscularly every six hours for five days for a total dosage of 20 Gm. Penicillin was administered in divided doses to those patients secondarily infected and to those with concomitant syphilis. Four patients underwent partial or total vulvectomy following adequate therapy and a suitable period of maximal healing. Subjective improvement was noted in twenty-four hours with objective healing in forty-eight hours and complete healing in ten days to two weeks after cessation of therapy. One patient suffering from granuloma inguinale, lymphogranuloma venereum, and syphilis was unable to procure streptomycin and was treated with penicillin, sulfathiazole, and Fuadin, followed at a later date by simple vulvectomy. No toxic reactions were noted except for two patients who complained of mild vertigo.

Case 1.—T. J., aged 23 years, first noticed a lump arising on the vulva in January, 1945. The lesion was excised and she remained in the hospital for two months postoperatively receiving penicillin and bismuth. In June, 1946, a cesarean section was performed because of "sores" on the vulva. One month later the lesions became extremely painful and the labia markedly edematous. She received treatment with Fuadin and bismuth followed by forty-five injections of tartar emetic. The continued pain and lack of healing caused the patient to attempt suicide upon two occasions.

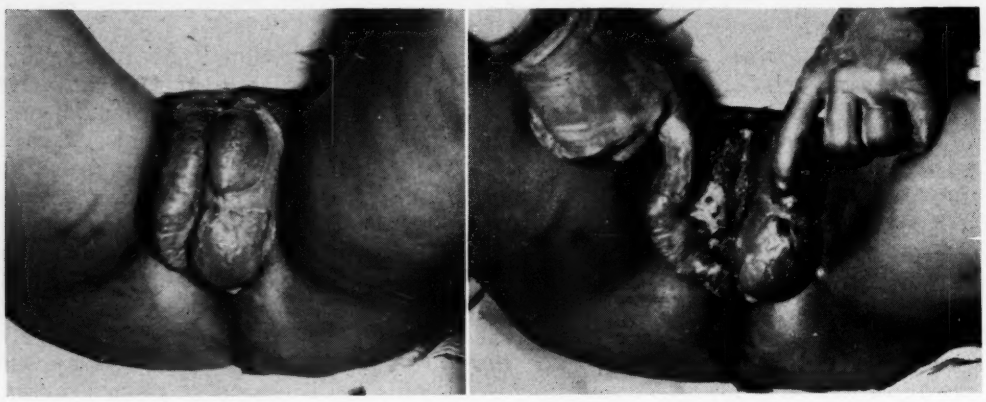

Fig. 1. Fig. 2.

Figs. 1 and 2.—T. J. Nov. 9, 1947. Granuloma inguinale before treatment.

She was first seen by us in November, 1947, at which time the vulva was markedly edematous with numerous ulcerating lesions covering the entire area. The lesions were deep red in color, granular in appearance, and covered with grayish exudate. Two days

following the instigation of streptomycin the pain had subsided and the lesions were becoming dry and changing to a dull red hue. Two months following treatment all evidences of infection had disappeared but the labia remained markedly hypertrophied. Simple vulvectomy was performed removing the labia majora, labia minora, and the mons veneris. Postoperatively, the patient received 9.5 Gm. of streptomycin and 1,900,000 units of penicillin intramuscularly in divided doses; infra-red radiation and triple sulfonamide cream were used locally. No Donovan bodies were present in the excised tissue. Frequent follow-up examinations over a period of eight months have revealed no evidence of recurrence.

Fig. 3. Fig. 4.

Figs. 3 and 4.—T. J. Jan. 19, 1948. After treatment with streptomycin.

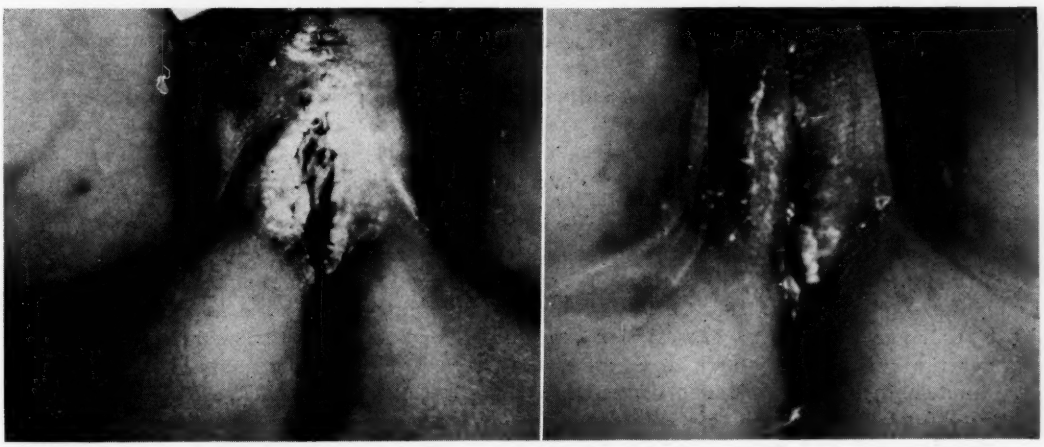

Fig. 5. Fig. 6.

Fig. 5.—T. J. Jan. 29, 1948. Eight days postoperative.
Fig. 6.—T. J. March 15, 1948. Six weeks postoperative.

CASE 2.—P. S., aged 47 years, had been treated over a period of twenty years at four teaching hospitals. Therapy had included the various antimonials, x-ray treatment, and an extensive course of sulfathiazole. Biopsy of specimen taken just prior to admission in June, 1947, revealed Donovan bodies within tissue cells. The lesions were serpiginous, ulcerative, and involved the entire vulvar and perineal areas extending into the vagina posteriorly for a distance of one centimeter.

Streptomycin was administered intramuscularly in 1 Gm. doses every six hours over a period of five days. The lesions rapidly healed and at the time of discharge three weeks later all evidence of infection had disappeared with significant decrease in the size of the involved area. One year later only pigment changes remain as mute testimony of the original infection.

CASE 3.—R. B., aged 21 years, first noted a "sore" 1 cm. in diameter on her genitals in April, 1944. Syphilis was diagnosed and treatment was administered. Daughter lesions soon appeared and spread over the vulva. These granulating lesions would repeatedly heal only to break down again and again. Hypertrophy of the labia was first noted in January, 1945, at which time she was hospitalized elsewhere and treated for syphilis, lymphogranuloma venereum, and granuloma inguinale.

The first admission to the Graduate Hospital was in October, 1947. The vulva, perineum, and introitus were covered with raw, granulating, painful lesions with indurated borders. The labia minora were so elephantoid they obscured all underlying anatomy. The left labium majus appeared uninvolved but the right was at least three times normal size. The clitoris was completely eroded. Twenty-four hours following the first injection of streptomycin pain had completely disappeared and ulceration had decreased. Four days later the lesions had decreased in size by 30 per cent. Within three months maximal healing had occurred and simple vulvectomy was performed. At the time of discharge twelve days postoperatively the wound area was completely healed. One week later the patient was readmitted because of two small ulcers in the incision; on divided doses of penicillin the infection immediately subsided and there is no evidence of recurrence one year later. No Donovan bodies were found in the removed tissues.

CASE 4.—L. J., aged 26 years, noticed a "cluster of bumps on the privates" eighteen months prior to admission. Six months later she was hospitalized and treated with penicillin for eight days but the lesions became progressively worse.

She was referred to the Graduate Hospital in November, 1947, at which time there was marked elephantiasis and painful ulceration of both labia majora. Forty-eight hours after streptomycin was started, the lesions were no longer painful and there was considerable decrease in the amount of exudate. Two days later definite crusting was evident and the inflammatory appearance had disappeared. The patient did not return for six months, at which time the only evidence of the original infection was a moderate residual fibrosis of the labia minora. Partial vulvectomy was performed in June, 1948, resulting in healing. The excised specimens revealed no Donovan bodies.

CASE 5.—F. W., aged 22 years, noticed a slowly rising bubo in the left groin in February, 1946. This was followed in a few days by a small ulcer on the left labium majus. The bubo became inflamed and burst spontaneously exuding blood and purulent material. Tissue specimens from bubo and ulcer were biopsied and the diagnosis of granuloma inguinale was established. Tartar emetic was administered and the lesions healed, only to recur one year later. These lesions did not respond to therapy but continued to spread over the entire vulvar area and extended posteriorly around the anus. Because of the granulomatous lesions, cesarean section was performed in March, 1947.

The first admission to the Graduate Hospital was in August, 1947. The lesions were extensive, red, and covered with a dirty exudate. The patient was seven weeks pregnant at the time of admission. The lesions responded immediately to 20 Gm. of streptomycin. One week after discharge the patient was readmitted and operated upon for ruptured left cornual pregnancy. At that time the lesions were completely healed. Examination one year later reveals only minute areas of depigmentation.

CASE 6.—A. D., aged 25 years, had noted increasing hypertrophy of the external genitals for two years prior to admission. Fissures were present between the labia, and the clitoris had been completely eroded. Velvety, red, exudative areas were found on the labia minora and on the inner aspects of the labia majora. The patient was emaciated, having lost fourteen pounds in the past year.

The diagnoses of granuloma inguinale, lymphogranuloma venereum, and syphilis were established by specific tests. As she was unable to procure streptomycin, she was treated with penicillin, sulfathiazole, and Fuadin. The lesions healed but more slowly than in those patients who were treated with streptomycin. Simple vulvectomy was performed six weeks later and there has been no recurrence during the past year. No Donovan bodies were present in the excised tissues.

Summary

1. Administration of 20 Gm. of streptomycin in 1 Gm. doses intramuscularly every six hours constitutes effective and apparently adequate therapy.

2. Penicillin proved effective against secondary invaders.

3. Four patients required partial or total vulvectomy following therapy.

4. None of these patients has had a recurrence in the six to twelve months which have elapsed since treatment.

5. Donovan bodies, present before streptomycin treatment, could not be demonstrated in the excised specimens.

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Aranson, Albert, and Dwight, Richard W.: Streptomycin in the Therapy of Tuberculosis of the Endometrium, New England J. Med. **240**: 294, 1949.

This report deals with the apparent arrest of endometrial tuberculosis consequent to treatment with streptomycin in a 26-year-old married woman, whose chief complaint was sterility. An endometrial biopsy revealed tuberculosis of the endometrium. Streptomycin, 0.5 Gm. intramuscularly every twelve hours, was begun and continued for one hundred twenty-nine days.

Following this therapy, endometrial biopsies were taken. No tubercles were found and there was no inflammatory exudate. Guinea-pig injection of one strip of endometrium resulted in negative findings on autopsy.

Culdoscopy at a later date revealed a normal-appearing uterus with fine adhesions about the ovaries. The tubes were not patent.

It is suggested that further trial of streptomycin therapy in endometrial tuberculosis is warranted. JAMES P. MARR.

STUDIES ON BETA-GLUCURONIDASE: I. ACTIVITIES IN HUMAN ENDOMETRIUM

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A FUNDAMENTAL role of b-glucuronidase in the physiological action of the estrogenic hormones has been previously proposed[1] on the basis of observations made in animals and in human beings. The increase in the glucuronidase activity found in the liver, kidney, and spleen of animals fed borneol and menthol[2] and the elevated glucuronidase in the uteri of castrate female mice receiving estrogenic hormones[3] could both be most readily explained on the basis of a synthetic action in vivo of the enzyme. In the first case, glucuronides of the terpenes and, in the second case, of the estrogenic hormones would be produced. Such a reaction was termed one of "metabolic conjugation" to differentiate it from the so-called detoxication reactions. In human beings, the serum activity of this enzyme increased approximately fourfold during pregnancy[4, 5] and was still higher during pre-eclamptic toxemia of pregnancy,[6] as well as during pregnancy associated with excessive water retention without hypertension.[7]

Since an increasing titer of serum and urinary estrogens occurs during the early course of the menstrual cycle, followed by a fall in the later part, it has occurred to us that b-glucuronidase activity in human endometrium might show similar cyclic variations. In this paper, the events of the menstrual cycle have been correlated with enzymic activity providing data which may be valuable in the future for comparison with various pathologic states affecting the uterus.

Material and Method

A total of thirty-six patients were studied. Except for three designated exceptions, these patients were judged to possess normal menstrual cycles. Their ages varied between 19 and 48 years, the interval in menses from fifteen to thirty-two days, and the menstrual flow from three to eight days.

Endometrial biopsies were obtained by a Novak suction curette, with the usual aseptic precautions. These tissues were transferred to glass weighing bottles equipped with stoppers and then were homogenized in water. The centrifuged homogenates were then assayed for b-glucuronidase activity, according to the method described by Fishman, Springer, and Brunetti.[8] Readings were made in duplicate. The amount of tissue assayed varied between 0.0332 gram and 0.1736 gram. b-Glucuronidase activity was expressed as the gamma phenolphthalein liberated per gram of tissue per hour. Histologic

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specimens of endometrium were prepared on two-thirds of the biopsies. The stain was a routine hematoxylin and eosin.

Results

In view of the fact that tissues were obtained from different subjects with variability in respect to age, interval in menses, and menstrual flow, it was to be expected that the results might show wide variations. For this reason, the data (Tables I and II) have been presented in tabular rather than in graphic form, in order to picture the events more accurately. For the same reasons, it was felt that numerical averages for endometrial glucuronidase at different periods of the cycle would have little meaning and so they have been omitted. However, definite changes in the data exist and these may be stated as follows: The range of glucuronidase activity in normal human endometrium was from 895 to 9,040 gammas of phenolphthalein per gram of tissue per hour. The lowest values for endometrial glucuronidase were found in the interval immediately preceding and following the period of menses. The highest values observed occurred most frequently in the interval between. These changes did not seem to be related to the event of ovulation judging from the lack of correlation of the glucuronidase values with the histologic appearance of the tissues.

TABLE I. ENDOMETRIAL TISSUE ANALYSES AND THE NORMAL MENSTRUAL CYCLE

IDENTIFICATION	AGE	PARITY	INTERVAL	FLOW	DAY OF CYCLE*	MICROSCOPIC APPEARANCE†	ENDOMETRIAL GLUCURONIDASE (UNITS PER GRAM)
392250	32	1	30	5	6	P	1,930
433707	28	1	27	5	6	P	1,440
419419	29	0	30	7	6		1,595
420391	30	0	28	4	6	P	2,200
433755	26	0	28	4	7		1,180
434577	29	0	15	5	7		3,345
433740	32	2	28	4	10	P	3,170
217884	31	3	28	5	10		5,385
358023	35	0	25	5	11		2,410
436761	30	1	28	5	11	P	2,600
74648	36	1	25	5	11	P	3,319
432504	33	2	30	7	13	P	5,350
431170	24	2	28	4	15	S	3,480
434571	35	0	28	8	16		4,079
130513	34	2	30	7	16		4,147
438061	25	0	27	5	16	P	5,522
406068	25	0	29	6	16	P	4,384
412438	19	0	30	5	18	P	3,720
419465	29	0	28	5	18	P	9,040
405405	23	2	30	5	20		3,559
169442	48	6	30	3	20	S	4,280
436767	28	1	30	5	22	P	5,710
420067	34	2	27	4	23	S	6,460
434544	20	0	25	4	24	S	1,868
185516	28	4	30	8	24	S	3,014
413974	28	0	28	6	24	S	8,725
260495	37	1	28	5	25		1,927
428896	30	2	32	4	25		8,080
430219	28	0	26	6	25	S	3,600
237171	29	0	26	5	26	S	4,687
385366	25	0	26	6	26	P	1,283
420893	28	0	30	4	27		1,514
432111	24	1	30	4	30	P	895

*Day of cycle refers to the number of days following the onset of menses.
†P = proliferative. S = secretory.

TABLE II. RELATION OF ENDOMETRIAL GLUCURONIDASE ACTIVITY TO TIME PRECEDING MENSTRUATION

DAYS FROM MENSTRUATION	14	13	12	11	10	9	8	7	6	5	4	3	2	1	0
Glucuronidase Activity (Units per gram)	2,410	3,480	4,079	5,522	9,040		3,345	8,080	3,014		6,460	1,927		1,868	1,283
	3,319	4,384	3,720		3,559		5,710				8,725	1,514		3,600	4,687
	4,147				4,280										895

Different patients. Data obtained from Table I.

According to Bartelmez,[9] single endometrial biopsies are not always statistically valid cytologic samples of the endometrium. It was desirable to determine if enzymic activity was also variable in the endometrium. Multiple specimens were obtained from extirpated uteri of the same patients and assayed independently. Table III list the findings. In spite of the variations observed, it was felt that these were not extensive enough to disturb the general pattern described above.

TABLE III. GLUCURONIDASE OF MULTIPLE SPECIMENS OF ENDOMETRIUM

IDENTIFICATION	DIAGNOSIS	GLUCURONIDASE ACTIVITY (UNITS PER GRAM)		
		NO. 1	NO. 2	NO. 3
425507	Menopausal bleeding	6,091	5,753	4,536
452215	Metrorrhagia	3,520	3,180	
400975*	Cesarean hysterectomy	670	465	

*The low values obtained from decidua near term have been a consistent finding.[15]

Comment

Frank and Goldberger[10] and others[11, 12] found an increase in blood estrogens during the normal menstrual cycle. Apparently two peaks in estrogen secretion occurred, one at ovulation and another during the luteal phase. During the last three to four days of the cycle, estrogen secretion rapidly falls off. The behavior of the b-glucuronidase activity of the human endometrium during the normal menstrual cycle is consistent with the changes in estrogen secretion reported. However, other factors in addition to estrogen may be influencing endometrial glucuronidase. The structural incorporation of glucuronic acid in various intracellular substances, such as mucins, may involve glucuronidase activity.* That glucuronidase is related to cellular proliferation or regeneration has been suggested by Kerr and Levvy,[13, 14] and it seems pertinent that during the proliferative phase of endometrial development considerable mitotic activity occurs, while during the late secretory phase cellular division becomes lessened.

It should be noted that in comparison with other nongynecologic human tissues,[4] uterine endometrium may be considered as being relatively rich in glucuronidase. In addition, glucuronidase activity is greater in normal human endometrium than in other normal gynecologic tissues (ovary, myometrium, cervix and vagina).[15] It is of interest also that Atkinson and Engle[16] have observed marked variation in the alkaline phosphatase of human endometrium with the menstrual cycle. They state that the enzyme is high during the proliferative phase, being reduced during the secretory phase, and disappearing before the onset of menstruation.

*Friedenwald and Becker, employing a histochemical stain, found glucuronidase activity in the glandular endometrial epithelium (J. Cell. & Comp. Physiol. 31: 303, 1948).

Summary

Endometrial biopsies (suction curette) were obtained from thirty-six different women at various stages of the normal menstrual cycle. These specimens were assayed for glucuronidase activity. An increase in the activity of this enzyme with the passage of time following the first day of menses was detected during the first two thirds of the menstrual cycle. The endometrial glucuronidase declined in the last interval of the cycle. Considerable variation was noted and could be explained in part by the character of the clinical material studied. The presence or absence of progestational endometrium seemed to play a role of little importance.

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Bishop, P. M. F., Kennedy, G. C., and Wynn-Williams, G.: Potency and "Toxicity" of Some Synthetic Estrogens, Lancet, p. 764, Nov. 13, 1948.

To compare the potencies of various orally effective synthetic estrogens, the authors have selected as a "therapeutic unit" that oral dose of drug which, when administered for fourteen consecutive days to amenorrheic women, produces withdrawal uterine bleeding within two weeks of the last dose. Nine hundred ninety-seven courses of estrogen were given to a group of 168 women, of whom twenty-two had primary and one hundred forty-six had secondary amenorrhea. Stability of response was demonstrated by repeating an estrogen course after a lapse of time, or after an intervening course of another estrogen.

A wide range of therapeutic units was encountered for each estrogen in different patients. However, the ratio between the effective doses of any pair of estrogens, determined on individual patients, was fairly uniform. Dienestrol is about one-fourth, doisynolic acid one-fifth, and hexestrol about one-eighteenth as potent as stilbestrol.

At the threshhold dose of each estrogen, toxicity (nausea) appeared in 39 per cent of stilbestrol cases, 6 per cent of dinestrol cases, 5 per cent of hexestrol cases, and 12 per cent of doisynolic acid cases. The increase of toxicity with dosage has been shown to be linear in the case of stilbestrol, and this rule is probably true in the cases of the other synthetic estrogens. Hence the relative toxicity of these drugs should be like that shown above, at any therapeutic level. Irving L. Frank.

X-RAY INCIDENCE OF FRACTURED CLAVICLE IN VERTEX PRESENTATION

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THE clinical diagnosis of fractured clavicle in the newborn has been made very infrequently on the obstetrical service, Sinai Hospital, Baltimore, Md. We, therefore, were curious to know how many silent fractures, fractures which gave no clinical evidence, were missed. The only way to determine this was to submit a consecutive series of infants to routine x-ray examination. However, before we did this, a survey of the current literature was made.

This survey revealed no studies similar to our own. The only investigation approximating it was that of Adler, 1928. He examined 2,000 newborn infants for fracture of the clavicle. Only one case was found on manual examination. However, he submitted 600 consecutive cases which showed no fracture to fluoroscopy, but no additional case was detected by this method. There are several papers dealing with the incidence of fracture of the clavicle as detected by routine postnatal physical examinations, the incidence varying from Adler's 0.5 per cent to 3.5 per cent. G. T. Hedberg, 1946, reports 86 fractured clavicles in 2,450 vertex deliveries (3.5 per cent); all were first detected on physical examination and later confirmed by x-ray film. Hedberg includes a thorough review of the literature in his study. Reither, in 1902, observed 65 fractures in a single year, but does not state how many deliveries were involved. Muus, in 1903, examined 1,700 newborn infants and found 22 fractures (1.4 per cent). In 1905, Hauch, at the same hospital, was able to reduce the incidence to 0.6 per cent by eliminating traction on the head to facilitate the delivery of the shoulders. Troitzkaja, in 1923, reported an incidence of 1.4 per cent.

All of the above studies agree that the accident is benign and no report of residual defect is noted. Fracture of the anterior shoulder predominates over that of the posterior shoulder. No noteworthy relationship to the size of the baby is reported; indeed, birth fracture of the clavicle has even been observed in premature infants. Curiously enough, the above reports showed a higher incidence of the accident in children of multiparas. The site of the fracture is uniformly at the junction of the middle and outer thirds of the clavicle. No bilateral fracture has been reported. No relationship to abnormality of the maternal pelvis or to difficulty of labor or delivery is described. The etiology is obscure; but it is generally agreed that the fracture occurs during the delivery of the shoulders, and not prior to it.

In our study, 300 consecutive, living, term babies who delivered by vertex, were examined by x-ray for fracture of the clavicle. Postpartum x-ray pelvimetry, using the Dippel-Hodges technique, was performed on the mothers of those babies who yielded a positive x-ray diagnosis. Five clavicle fractures were discovered (1.7 per cent). Not a single one of the five had even been suspected after the usual cursory examination in the delivery room and the thorough

pediatric examination in the nursery. In other words, they were all silent fractures. However, after the roentgen diagnosis, it was possible to obtain crepitation in each after prolonged manipulation.

In each case, the break was complete and occurred at the junction of the middle and outer thirds of the clavicle. In four of the five cases, overriding of the fragments was demonstrated by the initial x-ray film. On the basis of external rotation charted at delivery, the posterior shoulder was fractured in three cases, the anterior shoulder in one, and in the fifth case the side to which the back rotated was not recorded.

Four of the five mothers were primiparas and the other had had one previous full-term pregnancy. The five patients had clinically normal pelves. All were delivered with elective low forceps and episiotomy as is routinely practiced in this hospital. The delivery notes do not state if fundal pressure was applied to facilitate the stemming of the anterior shoulder under the symphysis pubis. Pertinent data of the maternal course in the five cases are outlined in Table I.

TABLE I

MOTHER								INFANT			
INCIDENCE IN SERIES	WARD OR PRIV.	PARITY	AGE	LENGTH LABOR	ANESTHESIA	TYPE DELIVERY	TYPE EPIS.	POSITION	CLAVICLE FRACTURED	BIRTH WEIGHT (GM.)	SEX
55th	P	00000	23	5 hr. 2 min.	Spinal*	ELF†	Median	OA	Left	3,298	M
84th	P	00000	21	9 hr. 10 min.	Spinal	ELF	LML	LOA	Left	3,604	F
187th	P	00000	23	7 hr. 45 min.	Spinal	ELF	LML	LOA	Right	2,815	M
273rd	P	11001	39	3 hr. 52 min.	Gas-oxygen-ether	ELF	Median	LOA	Right	3,206	M
296th	P	00000	20	12 hr. 18 min.	Spinal and gas-oxygen-ether	ELF	LML	ROA	Left	2,986	F

*50 mg. of procaine.
†Elective low forceps.

X-ray pelvimetry by the Dippel-Hodges technique obtained post partum showed two of the mothers to have mild degrees of midpelvic contraction. This was not reflected in the course of their labor. The x-ray measurements are given in Table II.

TABLE II

CASE	OBSTETRICAL CONJUGATE (CM.)	TRANSVERSE INLET (CM.)	BISPINOUS (CM.)	POST. SAGGITAL OF MID PELVIS (CM.)	BITUBEROUS (CM.)
55th	11.6	11.4	8.7	3.6	10.2
84th	12.7	12.6	9.8	4.1	10.1
187th	12.9	12.4	12.9	3.5	12.5
273rd	13.2	12.2	10.4	4.5	12.4
296th	12.6	12.1	Not obt.	3.7	10.8

On initial examination in the nursery, all five infants were found to have normal skeletal systems. No limitation of motion or swelling in the region of the clavicle was noted. All had a positive Moro reflex. After x-ray detection of the fracture, and manipulation of the fractured part until crepitation was felt, some limitation of motion in the affected arm was noted. The firm swelling of callous formation was observed on discharge examination of the infants in Cases 55 and 187, who were discharged on the ninth and seventh days of life. The infants in Cases 84, 274, and 296 were discharged at ages 6, 6, and 8 days, respectively, and no callus was demonstrable. Four of the five infants received no orthopedic therapy and the other was put in a modified Velpeaux-type dressing during the hospital stay.

Follow-up information obtained four months after delivery from the pediatricians who were in contact with the cases revealed that in no incidence was there any residual deformity or limitation of motion.

The number of clavicle fractures diagnosed clinically without routine x-ray examination is of interest. Since this study was completed, all newborn infants have been examined on discharge from the hospital by one of two members of the pediatric house staff. Attention has been focused on this injury and it was specially looked for in each case. In the 655 vertex deliveries occurring between the termination of these studies and this writing, only one fractured clavicle has been diagnosed clinically. This is an incidence of 0.2 per cent.

Summary

1. One and seven-tenths per cent of 300 full-term infants born by vertex deliveries had silent fractures of the clavicle as determined by routine x-ray examination.

2. None of these was recognized clinically prior to the x-ray examination.

3. X-ray pelvimetry on the five mothers showed no significant abnormality.

4. This injury heals spontaneously without treatment.

5. No residual deformity or limitation of motion resulted from these fractures.

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Trites, A. E.: The Significance and Management of Fibromyomata Complicating Pregnancy, Canad. M. A. J. **59**: 539, 1948.

The author reports a total of eighty-seven patients with myomas of the uterus complicating pregnancy (4.7 per cent) between 1936 and 1948. The most common complication occurring in these cases during pregnancy is degeneration with all of its attending symptoms. Severe necrobiosis or torsion of a pedunculated tumor may necessitate surgical intervention. Toward the end of pregnancy every effort should be made to temporize. In these eighty-seven cases, thirteen abortions and nine premature labors occurred. Dystocia may be produced by large myomas as a result of obstruction of the birth canal. The incidence of cesarean section was 18 per cent, but only in 12.5 per cent were the myomas responsible for the section either directly or indirectly. In the author's hands, hysterectomy during cesarean section has definite advantage over myomectomy. The patients have a smoother convalescence. The exception to this is in the young primipara in whose case conservatism is the procedure of choice. Morbidity was present in twelve patients in this series. The aftertreatment of the parturient woman with fibroids can be along expectant lines with the indication for operation being on the same basis as for fibromyomas in general.

WILLIAM BERMAN.

A PRELIMINARY REPORT ON A NEW CONCEPT IN THE TREATMENT OF RH-NEGATIVE PREGNANT WOMEN

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GREAT strides have been made during the last few years in the correlation of the Rh factors as antigens with erythroblastosis fetalis. Many remedial measures of attacking this problem are in vogue today. Most of these are aimed at counteracting, as far as is possible, the injury already incurred, by treating the affected but living newborn. In April of 1946 we began a series of studies with the emphasis on prevention of this complication, if possible.

The hypothesis exists that in order for the mother to develop antibodies against the Rh factor, there must me a transfer of the antigen from the fetal circulation through the placental villi. If the above assumption is correct, then any means which would tend to prevent the transfer of these antigens would in a great part prevent erythroblastosis fetalis. It has been further reasoned that some of the causes of bleeding and abortion occurring in many women were an increased uterine contractility or some abnormality, functional or organic, present in the placenta or its uterine base. It is well known that Rh-negative women have a greater tendency during pregnancy to uterine contractility and to bleeding and early abortion.

With these basic ideas in mind, we herewith submit a preliminary report on a series of fifty Rh-negative pregnant women cared for by us from April, 1946, to Nov. 1, 1948. In all cases in this series the pregnant mother was Rh negative and the father was Rh positive. At the present time some of the infants delivered have not been typed. All Rh tests were made in the Marysville Clinic Laboratory and were rechecked and confirmed by the clinical laboratory at Stanford University Medical School in San Francisco. All tests for antibodies, blocking and agglutinating titers, were carried out at the Stanford University Laboratory.

Material

The patients studied to date include twenty-nine multiparas treated and delivered, five primiparas treated and delivered, twelve multiparas undelivered and under treatment, one primipara undelivered and under treatment, and three multiparas untreated and delivered.

The women listed as "treated" were given (1) anhydro-hydroxy-progesterone, 10 mg. orally daily, with exceptions mentioned later, and (2) vitamin K, 4.8 mg. intramuscularly weekly, beginning as soon as the tests were confirmed, and continuing until delivery. The average period of treatment was four and one-half months. Those listed as "untreated" either refused treatment or presented themselves for maternity care too near term to make test therapy worth while.

All treated patients with negative antibody tests when first seen remained free of antibodies to term. There were no cases of erythroblastotic infants or infants carrying greater than normal erythroblast count delivered to treated patients.

Three multiparas showed antibodies at the time of their first visits. These patients still under treatment, were given 30 mg. anhydro-hydroxy-progesterone daily and 4.8 mg. vitamin K intramuscularly weekly.

Their serologic studies are shown in Table I.

TABLE I.

		Rh′		RH_0	
	DATE TESTED	BLOCKING	AGGLUT.	BLOCKING	AGGLUT.
Case 1 (Z. T.)	7/10/48	1:512	1:32	1:32	1:4
	8/ 4/48	1:32	0	1:16	0
	9/13/48	0	0	0	0
	10/20/48	0	0	0	0
Case 2 (M. S.) (Sister of Z. T., Case 1.)	6/ 7/48	1:8	0	1:16	0
	9/ 9/48	1:4	0	1:8	0
	10/21/48	1:4	0	1:4	0
Case 3 (F. N.)	8/26/48	0	0	1:16	0
	11/ 1/48	0	0	0	0

One treated patient, a multipara, with doubtfully positive titer on initial visit, at term had a negative titer.

Although the quantity of antibody is expected to drop somewhat normally unless further transfer of antigen takes place, in these cases the titer continued its drop consistently and developed no rise in any titer subsequently.

In this series there were three untreated patients, multiparas, all of whom showed antibodies at term.

CASE 1.—F. F. delivered an infant whose blood showed numerous erythroblasts. The infant died a few hours after delivery. Autopsy findings were those of icterus gravis. The mother's blood tested an Rh_0 titer of 1:32 and Rh′ agglutinating antibodies of 1:4 six days after delivery. This mother has offered to attempt another pregnancy under treatment.

CASE 2.—E. J. gave a history of the death of her second baby with severe jaundice one week after delivery. At the end of her third pregnancy she delivered an infant with symptoms of erythroblastosis, including jaundice, anemia, palpable spleen, and with a blood smear having 103 erythroblasts per 100 white blood cells. The infant was given several blood transfusions and other supportive treatment and survived. The mother's blood gave a blocking titer of 1:64 eight months after delivery.

CASE 3.—T. G. delivered an apparently normal infant having one erythroblast per 100 white blood cells. The mother's blood showed an Rh′ blocking titer of 1:16 and Rh″ blocking titer of 1:8 ten days after delivery.

A detailed report of these cases and others still under study will be made at a future date.

Summary and Conclusions

1. No treated patients delivered erythroblastotic infants or infants with abnormal erythroblast count.

2. No treated patients who were free of antibodies on first examination developed any antibodies in the course of their pregnancies.

3. Those patients who did show antibodies on original tests under treatment showed a steady diminution or disappearance of antibodies without any subsequent rise in titer.

4. Three out of three untreated patients developed antibodies during pregnancy.

5. Two out of three untreated patients delivered erythroblastotic infants. One of these infants died.

6. In this series the use of anhydro-hydroxy-progesterone and/or vitamin K appears to have a definite effect on controlling erythroblastosis fetalis.

The authors realize that this is a relatively small series of cases, but that the results are sufficiently suggestive to warrant a preliminary report so that the results may be verified by other observers.

Medication used was Pranone (Schering), part of which was generously supplied by the company, and Hykinone (Abbott Laboratories), part of which was supplied by the company.

725-4TH STREET

Murphy, Douglas P., and Farris, Edmond J.: Treatment of Sterility: Insemination Timed by Rat Ovulation Test, J. A. M. A. 138: 13, Sept. 4, 1948.

This test was employed in order to predict the day for the insemination in a series of thirty-two women. Each couple that sought assistance was studied from three points of view: (1) sperm status of the husband, (2) patency of the Fallopian tubes, and (3) character of the wife's ovulation process. Fifty-seven inseminations were done on thirty-two women. Ten resulted in conception. Eight of the ten women conceived as a result of the first treatment; the remaining two women conceived on their second insemination. Forty-seven inseminations failed in their objective. Thirty-seven (79 per cent) of the forty-seven failures were charged either to an inadequate number of moving sperm cells or abnormal ovulation. Each of these two categories was predicted before the insemination was performed. Each patient had an insemination only once each month. It is important to note that eight of the ten conceptions followed the first insemination which speaks well for the rat ovulation test as a method for predicting the day when the egg is ready for fertilization. The authors noted a high incidence of low sperm counts and abnormal ovulations in this series. WILLIAM BERMAN.

Polak, Stanley S.: The Xenopus Pregnancy Test, Canad. M. A. J. 60: 159, 1949.

The Xenopus frog has large ovaries which occupy the greater part of its abdomen and eggs are present in them during the entire year. Eggs are never extruded except through stimulation by the male during the mating season or by injection of hormones. The test is based on the extrusion of eggs from two to twelve hours after the injection of urine concentrates containing gonadotropic hormone into a female Xenopus. If eggs are deposited, the patient is pregnant; if no eggs are extruded, the test is negative. The author found this test positive in 98 per cent plus of his cases. It is important that all drugs, even aspirin and hypodermics, should be avoided for at least two days prior to the test. WILLIAM BERMAN.

A STUDY ON FIRST-DAY AMBULATION IN OBSTETRICS

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THE object of this paper is to point out the advantages of ambulating obstetrical patients on or before the first postpartum day. There has been widespread and enthusiastic acceptance of surgical early ambulation and yet, in many quarters, one sees great reluctance to apply these principles to the obstetrical patient. Moreover, it is somewhat distressing to us to see "early ambulation" being started as late as the second and third postpartum days when its chief benefits have already been lost.

This paper will not review the history or principles of physiology of early ambulation so well expressed by Leithauser[1] and others. The sludged blood phenomenon which has been described by M. H. Knisely and co-workers[2] in various disease and traumatic states in the laboratory animal and in man seems to have a direct bearing in an explanation for the need of immediate early ambulation. Cornell and Mullen[3] reported their favorable experience by ambulating on the fourth postpartum day. We shall endeavor to show how much more effective earlier ambulation is in hastening recovery and preventing complications post partum.

At St. Joseph's Mercy Hospital we have been so gratified with the results of first day postpartum ambulation that we feel a statistical study has been more than warranted. The first-day ambulations when started here in 1941 were routine in unselected patients of several of our attending physicians. The enthusiasm of the patients and the excellent clinical results observed in these patients forced us to adopt in September, 1947, first-day ambulation as a matter of routine for all obsterical patients.

As a sampling of our experience, we present the first 1,010 patients delivered at or near term in the year 1947. This includes twenty-six cesarean sections. Of these, 434 were ambulated on or before the first postpartum day, 354 ambulated on the second or third day, and 222 started walking on or after the fourth day. We choose to call these groups, respectively, "early," "delayed," and "late" ambulations. The time of ambulation in these cases was dictated by the routine order of the physician in attendance. By our definition the first postpartum day starts at midnight after delivery. In the early group the average time of beginning ambulation was nineteen hours after delivery.

At this time the nurse in charge gives the patient a short explanation of what we mean by early ambulation. In bathrobe and slippers she is assisted to stand beside the bed and walk to a near-by chair where she is permitted to sit for three minutes before returning to bed. She is encouraged to be active in bed, and ambulations are repeated, progressively increasing the frequency and

length of time the patient is up and walking. By the third day she spends at least two hours a day up and about and performs her toilet in the bathroom. There she is provided with sterile pads, cotton, and paper toilet-seat covers and is instructed in their proper use. We use bedpans occasionally on the second postpartum day, and almost never after the third day

The accompanying table shows the trend and reflects the value of restoring the delivered patient to normal activity status as quickly as possible. The overall incidence of complications was three to four times less frequent in the early rising group than in the delayed and late groups. Not only was thrombophlebitis prevented, but the occurrence of all the incidental infections was definitely reduced. Our clinical impression of increased general well-being is supported by the reduction in morbidities of unknown etiology. The distinct decrease in infections of the episiotomy wounds and in the acute urinary tract infections should be noted. Cases of previous urinary tract pathology were excluded.

In the immediate ambulation group there was one case of massive atelectasis. This occurred three hours after classical section under ether anesthesia. Immediate bronchoscopic aspiration cleared the obstructive mucous plug, and ambulation was started five hours later. The patient recovered uneventfully.

The clinical data are shown in Table I.

TABLE I. AMBULATION GROUPS

COMPLICATIONS	EARLY (434)		DELAYED (354)		LATE (222)	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Subinvolution	1	0.23	4	1.13	4	1.80
Endometritis	2	0.46	8	2.26	9	4.05
Thrombophlebitis	0	0	1	0.28	3	1.35
Phlebothrombosis	0	0	0	0	1	0.45
Episiotomy infection	1	0.23	5	1.41	5	2.25
Incision infection	0	0	0	0	1	0.45
Wound separation (episiotomy)	1	0.23	0	0	1 (section)	0.45
Pulmonary embolus	0	0	0	0	0	0
Acute infection urinary tract	4	0.92	5	1.41	5	2.25
Acute mastitis	0	0	0	0	1	0.45
Morbidity of unknown etiology	9	2.07	22	6.20	8	3.60
Pneumonia	0	0	0	0	1	0.45
Atelectasis	1	0.23	0	0	0	0
Total	19	4.38	45	12.71	39	17.57

Of the twenty-six patients delivered in this series by section, twelve were in the early ambulation group, ten in the delayed, and four in the late. Four complications occurred. The only one in the early group was the case of atelectasis already mentioned. In the delayed group one patient developed an endometritis. In the late group one patient had a moderate fever of unknown etiology and one had a wound separation which required secondary closure. Here our figures per se are not significant but the trend is. The cesarean section patients in our experience do better and recover more rapidly if ambulated early. The prerequisites to early ambulation after section are anatomic approximation of all layers including the transversalis fascia and the use of minimal anesthesia. All but two of these sections were done under spinal or caudal anesthesia. Ambulation in these cases is managed in the same manner as in the routine obstetrical patient.

In this series of 1,010 cases, half (508) were delivered by specialists evenly distributed in these three groups. The incidence of complications in their hands was 10.04 per cent, while their less well-trained colleagues had essentially the same rate, 11.75 per cent. Spinal anesthesia was used in 49.08 per cent of the early group, 46.9 per cent of the delayed group, and in 40.54 per cent of the late group. The factors of special training and anesthesia, therefore, have little weight in the comparison of these groups.

We feel strongly that first-day ambulation in no way increases the incidence of subinvolution, rectocele, cystocele, or malposition. To the contrary, immediate ambulation seems to promote physiological restoration as evidenced by the marked reduction in incidence of subinvolution and endometritis occurring in the immediate puerperium. While we are not prepared to prove it statistically at this time, we find no basis for the condemnation leveled by some against early ambulation on the premise of tragic relaxations, etc., to occur in later years.

The complications of ambulation per se are essentially nil. Syncope is a rarity, never persists, and indicates only that the patient must be attended in her ambulation for a longer period of time. Spinal headache is intensified somewhat by ambulation, but its duration is unaltered. Approximately 80 per cent of our patients at present (47 per cent in this series) receive terminal minimal spinal anesthesia, and the incidence of the spinal type headache in repeated groups regardless of technique and medication used, ambulated or not, has been 10 ± 2 per cent. This presents no contraindication to ambulation. Severe hemorrhage (until controlled and the anemia corrected), Grade IV cardiac failure, and severe toxemia of pregnancy in general contraindicate ambulation early.

Summary

We have presented 1,010 patients delivered at or near term with whom routine ambulation was started on different days. Those ambulated on or before the first postpartum day had four and five times, respectively, fewer complications than those ambulated on the second and third days or the group up and about on and after the fourth postpartum day. The evidence of decreased incidence of infections incidental to the puerperium is striking, and the proof of earlier restoration of normal physiological function seems inescapable.

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Martzloff, Karl H., and Manlove, Charles H.: Vaginal and Ovarian Metastases From Hypernephroma. Report of Case and Review of Literature, Surg., Gynec. & Obst. **88**: 145, 1949.

The authors report a case of hypernephroma of the left kidney, the first symptom of which was bleeding from vaginal metastases. They present a review of all the previous literature on this syndrome. This case presumably represents the twenty-third instance of vaginal metastases complicating hypernephroma, without kidney symptoms. All patients with such metastases had an unfavorable outcome. The authors have assumed from their own and from evidence in the literature that metastases occur via venous channels. It is suggested that, if similar cases are observed with unsymptomatic hypernephroma, investigation of the left kidney be carried out. L. M. Hellman.

A SIMPLE, ACCURATE PREGNANCY TEST

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THE physician frequently is confronted with a patient whose menses are a few days overdue. Often it is important to establish the presence or absence of a pregnancy in such a patient. The conventional animal tests usually are not sufficiently sensitive to detect a gestation of less than a month's duration. The chemical tests are, in general, not reliable. Furthermore, the above tests are not simple and require considerable equipment. The skin tests for pregnancy are simple enough, but the results are not accurate in the hands of most investigators.

The treatment of delayed menstruation with Prostigmine was first introduced in 1940.[1] Since then, a number of physicians have confirmed the ability of Prostigmine to induce a flow of blood in most nonpregnant women with delayed menses.[2-4] One, however, is impressed that bleeding often will not ensue if the patient has a glandular dysfunction, amenorrhea of more than a few weeks' duration, or is in the menopausal age group. Hence, the use of Prostigmine as a pregnancy test, although it is of value and a step in the right direction, still leaves much to be desired.

In 1942 Zondek[5] described his treatment for secondary amenorrhea of less than two years' duration. A high degree of accuracy was obtained by him and later by other investigators.[6, 7] The patient receives 15,000 rat units (2.5 mg.) of estradiol benzoate and 12.5 mg. of progesterone daily for two days. She will bleed several days after the last injection.

To the author's knowledge, no one has published any results concerning the use of estrogen and progesterone as a pregnancy test. It has been proved that the nonpregnant woman would bleed several days following the last injection. There is no reason to feel that the pregnant woman would bleed following the injections, since estrogen and progesterone, both individually or together, are being used to prevent the pregnant woman from aborting.[8-11]

Since 1946 the author has been using injections of estrogen and progesterone as a pregnancy test. To increase the percentage of nonpregnant amenorrheic women who would bleed following estrogen-progesterone injections, three injections were given instead of the two advocated by Zondek. Specifically, an ampule of Prometron (Schering) was injected daily for three days. Each ampule consists of 15,000 R.U. (2.5 mg.) estradiol benzoate and 12.5 mg. progesterone. The nonpregnant woman should bleed within a week following the last injection. The pregnant woman should not bleed. Fifty-six patients were subjected to the test with 100 per cent accuracy, one possible exception to be

noted hereafter. Twenty-six were not pregnant, and all bled. Thirty were pregnant, and none bled, except for one who spotted scantily on the fifth day following her last injection. The spotting ceased promptly and was too slight to cause confusion in the interpretation of the test. This patient is now seven months pregnant. Her only other pregnancy had resulted in a spontaneous abortion.

Nonpregnant Patients

The injections were given to twenty-six women who proved not to be pregnant. All of the nonpregnant patients menstruated from two to seven days following the last injection, with most requiring four or five days. The patients varied in age from 15 to 44 years. Fourteen of the twenty-six had had regular menses, and to be late with their period was most unusual. Twelve had had irregular menses, and to be late was not uncommon. The majority of the patients were less than two months overdue with their menses. Thirteen were two weeks late or less. No one in the series was over six months late. One woman was two and one-half months post partum, had not menstruated since delivery, and was concerned about the possibility of being pregnant again; she menstruated five days after the last injection. Several patients were near the menopause or had an endocrine disturbance and would not be considered satisfactory candidates for induction of bleeding with Prostigmine.

The type of flow was not significantly altered following the injections. Only four women felt that the flow induced was definitely heavier than their usual menses. None of these women had an enlarged uterus. While the possibility of an early abortion in these four cases cannot be excluded, it seems most unlikely. None of the nonpregnant patients in the series failed to bleed following the injections. The result probably would not be as good in amenorrhea of more than six months' duration.

Pregnant Patients

The injections were given to thirty women who proved to be pregnant. None of these patients bled following the injections except for one who spotted very scantily on the fifth day after the last injection. There was no other bleeding, no pain or cramps, and the pregnancy continued in an uneventful manner; at the time of this writing the patient is two months from term. One patient aborted two months after the injections; the abortion was probably due to a defective ovum since no fetus was present in the intact sac. Another patient delivered an immature infant four months following the injections. Because of the long interval between the injections and the loss of the pregnancy any cause and effect relationship seems most improbable. The other twenty-eight patients of this series have delivered or are near term. The ages of the patients varied from 22 to 40 years. Several of the patients presented sterility problems. Two had aborted twice. The shortest duration of the pregnancy in any of the injected patients was about two and one-half weeks, several patients being only a few days late with their menses. In most instances the menses were two or three weeks overdue. The longest duration of any pregnancy prior to the injections was about nine weeks.

Women with more advanced pregnancies were not injected, because a pregnancy of more than six weeks' duration usually can be determined clinically. There is no reason to feel that the injections will cause abortion, miscarriage, or premature labor in a pregnancy more advanced than any studied in this series. One patient with a positive pregnancy test by injection in the third week of her pregnancy was submitted to the Hogben frog test. The frog test did not become positive until the fifth week of the pregnancy, which was two weeks after a positive diagnosis had been made by estrogen-progesterone injections.

Comment

The use of large daily dosages of estrogen and progesterone for three consecutive days appears to be an accurate test for pregnancy. If the patient is not pregnant, and the amenorrhea is not over a few months' duration, she will bleed within a week following the last injection. If the patient is pregnant, she will not bleed following the injections. To maintain a high degree of accuracy, it is not recommended that women with amenorrhea of more than about six months' duration be submitted to this test. The method obviously may cause confusion if the patient is bleeding before the injections are started, or if the patient has an ectopic gestation. It is not recommended as a diagnostic procedure in these cases.

The danger of causing abortion appears to be nil. Large doses of estrogen alone or in conjunction with progesterone are being used to prevent abortion, as has already been stated. Van Wagener and Morse[12] gave 35 rhesus monkeys daily large doses of estrogens. In no case was abortion produced by the withdrawal of the hormone. Karnaky[8] gave pregnant women large doses of estrogen without producing abortion during the administration or by the sudden withdrawal.

The cause for hormone withdrawal bleeding is not clear. Finkler[7] used two injections instead of three, and investigated the endometrium in nonpregnant women before and after injections. She found that the two injections produced no significant change in the endometrial pattern. Estrogen and progesterone, alone or together, will produce hormone withdrawal bleeding. Engle[13] says: "The hormone withdrawal theories must assume that during the interval between withdrawal of the hormone and the actual hemorrhage something happens in the tissue of the endometrium. One of the effects of this something is the constriction of the base of the endometrial coiled arteries with resultant ischemia. Another concomitant effect is the apparent dehydration of the stroma. The actual bleeding appears to be a result of these conditions." This something that happens in the nonpregnant endometrium does not happen in the pregnant. Apparently the fear of inducing abortion has prevented the earlier use as a pregnancy test of the principle of hormone withdrawal bleeding.

The author does not maintain that he has arrived at the ideal dose in the use of estrogen and progesterone as a pregnancy test. He does feel, that in the method described in this paper, estrogen and progesterone can be used safely and accurately to diagnose intrauterine pregnancy in a patient with amenorrhea of less than six months' duration. It is plausible that the doses can be modified to advantage. The use of crystalline estrogen might shorten the number of injections. It is also interesting to speculate on what the combined effect of estrogen, progesterone, and Prostigmine would be on the amenorrheic patient. Such combinations too would seem to merit a trial as a pregnancy test.

Summary

1. The daily injection of 15,000 rat units (2.5 mg.) estradiol benzoate and 12.5 mg. progesterone for three days was used as a pregnancy test on fifty-six patients with amenorrhea of less than six months' duration.

2. Withdrawal bleeding was produced in all of the nonpregnant women. None of the pregnant patients bled except for one who spotted very scantily on one day.

3. The method described appears safe and accurate for use as a pregnancy test.

Most of the estrogen-progesterone used in this study was supplied by Schering Corporation.

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Diddle, A. W.: Endometrial Carcinoma, West. J. Surg., p. 20, Jan., 1949.

There are two flagrant errors regarding endometrial carcinoma widely held by the profession: that it is a rare disease, and that the prognosis is generally good. A study of 221 women of Dallas reveals that the average age of patients is 57 years. Only one was less than 30 years of age. The early symptoms are vaginal bleeding or leucorrhea, and the average time lost between the first symptom and diagnosis is 10.5 months.

Frequent use of inappropriate surgical procedures in treatment was the principal observation made from this study. Laparotomy without antecedent diagnostic curettage, indicating that cancer was unsuspected before operation often precluded proper use of preoperative irradiation. Ideal treatment consists of radium therapy followed in four weeks by total hysterectomy and bilateral salpingo-oophorectomy. This is subsequently followed by deep x-ray therapy. A five-year survival rate of 65 per cent to 75 per cent was obtained as a result of this procedure.

WILLIAM BICKERS.

Mandeville, F. B., Sahyoun, P. F., and Sutton, L. E., Jr.: Dysgerminoma of the Ovary in a 4-Year-Old Girl With Metastases Clinically Simulating Wilms' Tumor and Adrenal Neuroblastoma, J. Pediat. **34**: 70, 1949.

The authors report the case of a 4-year-old girl who died seventeen days after admission to a hospital. An autopsy revealed a bilateral dysgerminoma with rupture of left ovary, resulting in hemoperitoneum with metastases to left kidney and both renal glands, liver, pancreas, bone marrow of sternum and ribs, and lymph nodes, mesenteric, periaortic, and cervical.

Unfortunately, the pathological description of the tumor in this case report is inadequate. We miss the reference to the stroma of the tumor which is so typically described in Ewing's *Textbook of Neoplastic Diseases* as lymphoid in nature. The microphotograph accompanying the article suggests a glandular pattern, which is not typical of dysgerminoma. Therefore, the conclusions drawn by the authors concerning the treatment of the tumor should not be too seriously considered, particularly as the experience of other authors with the same type of tumor resulted in treating the tumor by conservative surgery. Such was the treatment of a granular-celi tumor in arrhenoblastoma, as advocated by Robert Meyer and E. Novak.

JAMES P. MARR.

AN INSTRUMENT FOR OBTAINING ADEQUATE CERVICAL BIOPSIES IN OFFICE PROCEDURES

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(From the Department of Obstetrics and Gynecology, State University of Iowa)

WITH the recognition that carcinoma of the cervix uteri can be diagnosed in its earliest stages only by histologic studies, adequate biopsies assume the utmost importance. It also follows that the technique of obtaining biopsies should involve a simple office procedure with minimal discomfort and risk to the patient.

The expression "adequate" biopsy is important. Small bits of distorted and denuded tissues taken from the cervix have long been the despair of pathologists. Many of the instruments used to obtain cervical biopsies are difficult to manipulate through an open speculum even under ideal conditions and almost impossible to use properly when the vagina is narrow or deep. In addition, it is often impossible to obtain any tissue, let alone multiple biopsies, from the junction of the squamous and columnar epithelium where most epidermoid carcinomas originate. The importance of obtaining multiple biopsies is best presented in Foote and Stewart's[1] report on the anatomical localization of carcinoma in situ of the cervix in twenty-seven patients. They have shown that a single biopsy specimen taken from either the anterior or posterior lip would have detected thirteen of the twenty-seven cases; biopsies from both the anterior and posterior lips would have found twenty of the twenty-seven; and biopsies from the anterior and posterior lips and both lateral angles would have detected twenty-five of the twenty-seven cases of carcinoma in situ in the series.

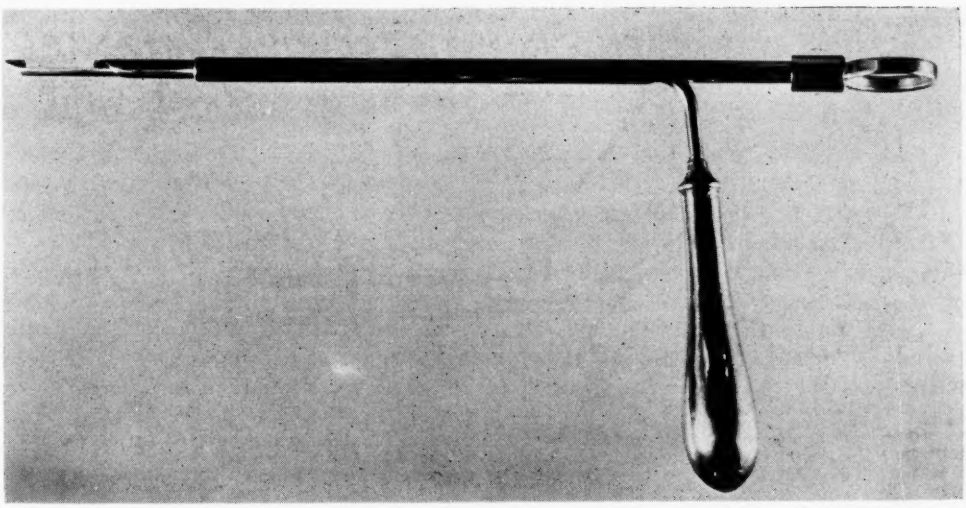

Fig. 1.—Photograph of the assembled biopsy instrument. Total length is approximately ten inches.

An attempt has been made to solve some of these problems by a device which enables the operator to obtain multiple thin, narrow, cleanly-cut strips of cervical tissue across the squamocolumnar junction. The assembled instrument is shown in Fig. 1.

The component parts are illustrated in Fig. 2. The instrument is essentially a hollow tube (1), one end of which carries the cutting blade. The circular blade (2) is made as a detachable portion of the tube and is attached by a tapered end which wedges firmly into the tube. A solid cylindrical core (3) fits closely within the tube. One end of the core serves as a guide for the cutting edge while the other is continuous with the handle of the instrument. The tip of the core is beveled for ease of insertion into the cervical canal. Just back of this beveled tip the upper surface of the core is cut away to form a recess. The length and depth of this recess determine the size of the specimen.

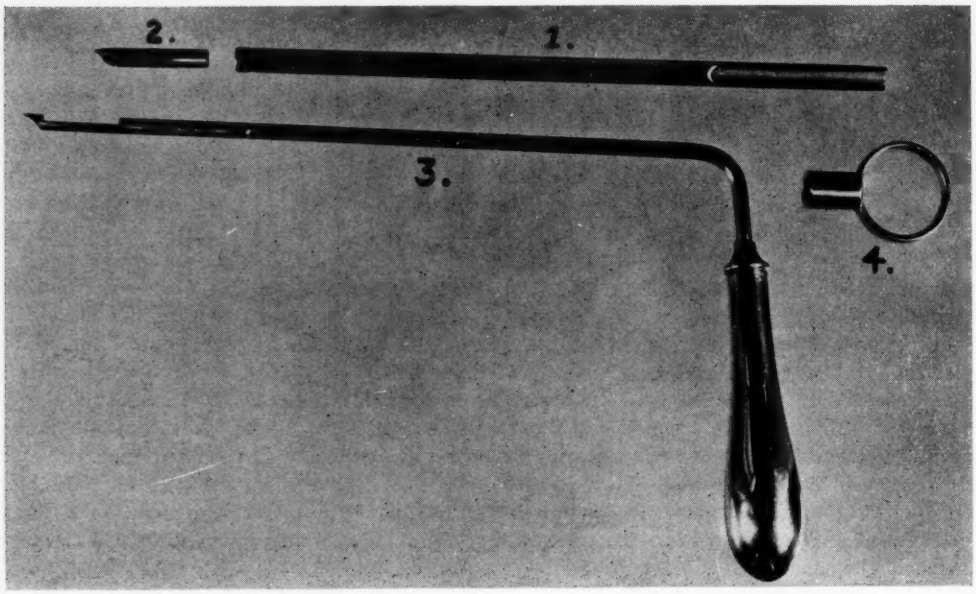

Fig. 2.—Photograph of the component parts of the biopsy instrument.

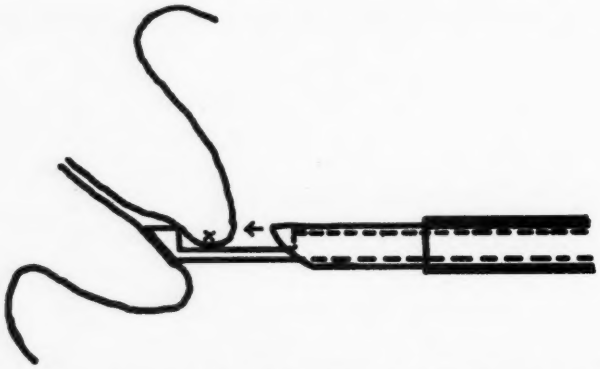

Fig. 3.—A schematic representation of the method of placing the beveled tip of the instrument into the cervical canal in order to obtain a biopsy specimen. The arrow shows the direction of thrust. The "X" marks the usual junction of squamous and columnar epithelium.

The motion of the cutting edge is limited in either direction by the length of a slot in the opposite end of the tube which slides over the angle of the central core and is closed at the back by the shank of the thumb ring (4).

All parts are chromium plated except the blade. It is necessary to remove the blade from the sterilizing solution at the end of each period of use and to apply a film of fine oil to prevent rusting.

The technique of using the instrument is simple. The tube, with the blade firmly attached, is pulled back until the entire recess is open. The tip of the instrument is then gently inserted into the cervical canal. By proper turning and tipping, the recess is pressed against the cervix at the site selected. Pressing the thumb ring forward cuts the tissue within the recess. The instrument with the blade full-forward is then removed. The thumb ring is pulled back and the entrapped thin strip of tissue is easily accessible. Tissue can be removed from several areas if so desired. When the vaginal smear shows abnormal cells and there is no visible cervical lesion, it is advisable to remove a thin slice from each quadrant of the cervix.

Fig. 3 is a schematic illustration of the instrument in position to remove a specimen from the anterior cervical lip.

This instrument has been in use during the past three months. No more bleeding, even following multiple biopsies, has been encountered than is usual after the use of office biopsy forceps. Cautery was required on one occasion, but a tampon placed against the cervix is usually sufficient to control bleeding.

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Curran, John F., Sr., and Healey, Thomas V.: Epidermoid Carcinoma Primary in Bartholin's Gland, New England J. Med. 240: 254, 1949.

The authors present a case report concerning a patient with a primary epidermoid carcinoma of the right Bartholin gland. Only seventy-five previous cases similar to this have been reported in literature.

After excision of the labial mass, a radical vulvectomy was performed and subsequently a bilateral Basset operation, with one week intervening between the operations. The inguinal dissection specimen consisted of areolar tissue, fascia, and muscle. The lymph nodes showed chronic lymphadenitis. Radiation therapy was considered unnecessary and the patient is being followed in the Tumor Clinic. JAMES P. MARR, M.D.

Speert, Harold: Carcinoma of the Endometrium in Young Women, Surg., Gynec. & Obst. 88: 332, 1949.

The author reports fourteen cases of carcinoma of the endometrium in women 40 years of age or under. This represents 5 per cent of all corpus cancers at the Roosevelt Hospital. For this reason the author stresses the point that any abnormal uterine bleeding not associated with pregnancy merits curettage prior to any other type of therapy. The author feels that these cases conform in general to a specific hormonal pattern characterized by long-continued and unopposed estrogenic activity. This is indicated, he feels, by low fertility and by the fact that there occurred in this group a high incidence of endometrial hyperplasia, cystic ovaries with no evidence of recent ovulation, and a high incidence of epidermidization of the cervical glands. L. H. HELLMAN.

IMPROVED EQUIPMENT FOR SUBSTITUTION TRANSFUSION IN THE NEWBORN WITH HEMOLYTIC DISEASE

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(From the Blood Bank and Research Division, Quincy City Hospital)

HEMOLYTIC disease of the newborn or erythroblastosis fetalis is in ninety-two instances out of one hundred caused by destruction of the infant's Rh-positive erythrocytes by maternal anti-Rh antibodies which entered the fetal circulation. For severely jaundiced infants, exchange transfusion based on drainage of the baby's blood and substitution with Rh-negative (rh) blood is the choice treatment.[1]

Three methods for replacement transfusion in the newborn are known: (1) In the sagittal sinus method,[2] the infant's blood is withdrawn from the longitudinal sinus, and the substitute blood is infused through a suitable superficial vein. (2) The radial artery[3] may be used for drainage of the infant's blood while the donor's blood is transfused through a vein. (3) The umbilical vein technique[4] makes use of a single blood vessel for both the withdrawal and the administration of blood.

The umbilical route is simpler than the other methods and therefore most frequently employed. Where a thrombus cannot be readily removed from the umbilical vein one of the other two routes is used.

The danger of infection through the umbilical cord is somewhat greater than in the other methods. However, antibiotics are administered after a substitution transfusion regardless of the technique employed.

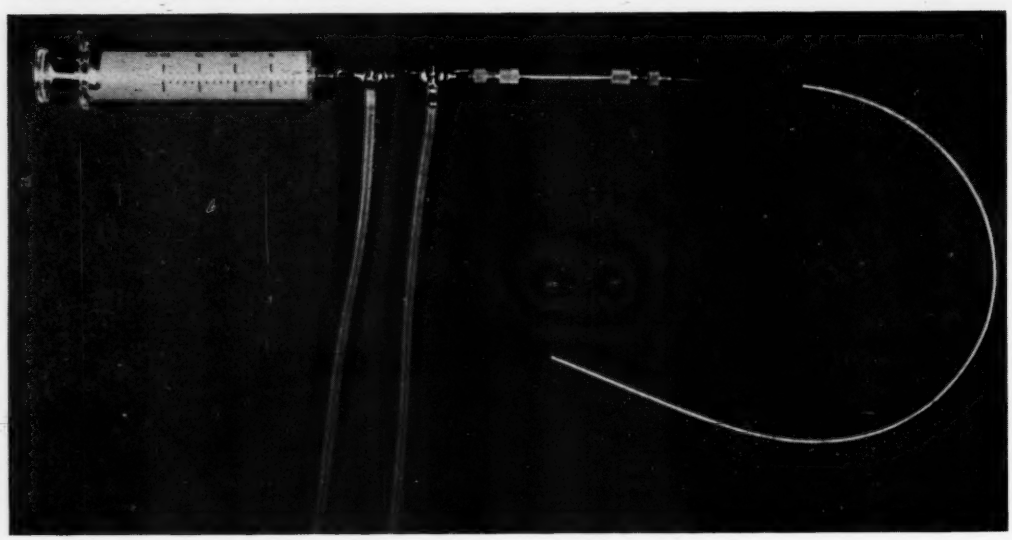

Fig. 1.—Single-unit transfusion set (old).

The greatest disadvantage of the umbilical vein technique as practiced[5] lies in the fact that two three-way valves must be operated simultaneously and that the infant's blood repeatedly passes through the major portion of the equipment. A part of the transfusion set is thus constantly contaminated by the infant's blood. Particles of the baby's blood mix with the donor's blood within the tubing, valves, and the syringe. The set is illustrated in Fig. 1.

The difficulties can be largely eliminated by a simple modification of the equipment. A Y-shaped glass piece is added to the set. The stem of this piece is connected with the glass adapter of the needle which is inserted into the catheter. To the two arms of the Y-piece, tubing is attached leading to the discard bottle and to the infusion bottle, respectively. The original set is taken apart. The two valves are disconnected, and two separate syringes are used instead of one. With such modified equipment, both varieties of blood pass only through the needle and catheter which is inserted into the inferior vena cava. The arrangement is illustrated in Fig. 2.

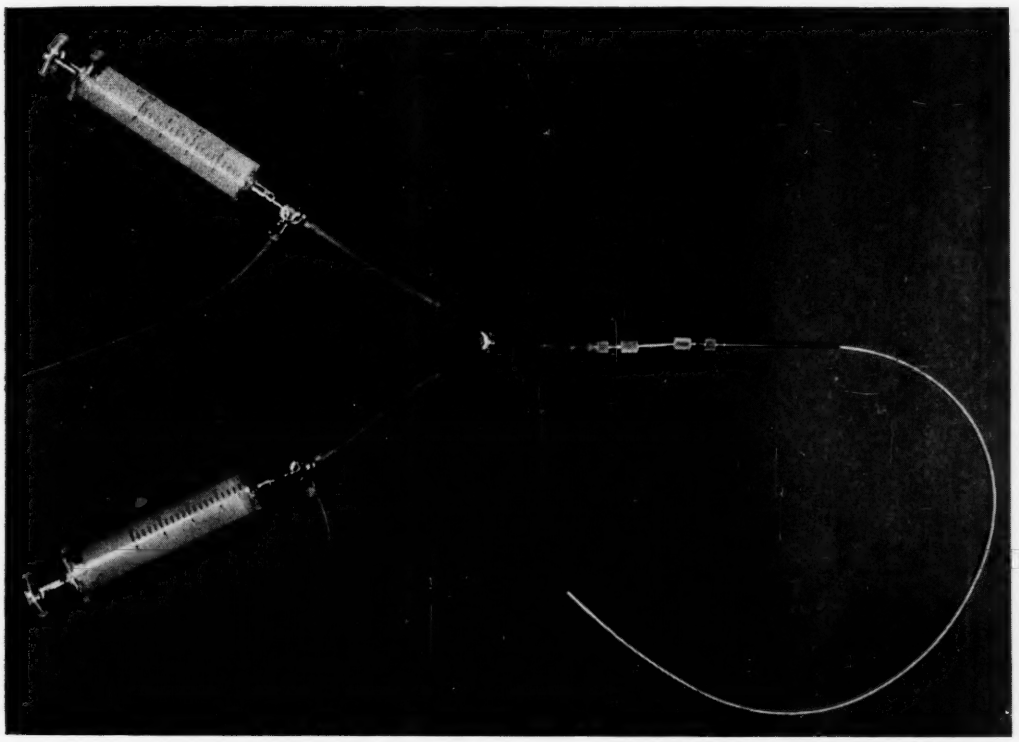

Fig. 2.—Two-unit transfusion set (new).

The donor's Rh-negative (rh) blood will still mix with the infant's Rh-positive (Rh) blood in the baby's circulation. Contamination of the major portion of the equipment will be eliminated, and reinjection of particles of the baby's blood will be prevented. Permanent separation of the withdrawal set from the administration set will facilitate cleansing of the equipment. Division of the equipment into two sets simplifies the procedure through individual operation of the valves. Elimination of multiple turns of the valves will speed up the replacement transfusion.

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TWO INSTRUMENTS FOR CERVICAL BIOPSY

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THE two instruments illustrated here have proved to be of helpful service in obtaining specimens for cervical biopsy after a trial of several months in detection clinic work. The first is a modification of the well-known Gayler uterine specimen forceps, embodying a different cutting-edge principle in the jaws of the instrument (Fig. 1). The edges of the grasping cups, instead of meeting in the closed position, are designed so as to telescope one into the other, giving a shearlike motion to the cutting edges. This not only greatly prolongs the sharpness of the cutting edges, but makes unnecessary any twisting and pulling motion in order to free the specimen. This telescopic action also grasps the tissue easily and avoids the sliding of the instrument over hard portions of the cervix. The instrument is 8½ inches in length. The other modification is the use of a heavier flat shank, which makes for more powerful application of the instrument for cutting, and the angulation of the handle for better visibility.

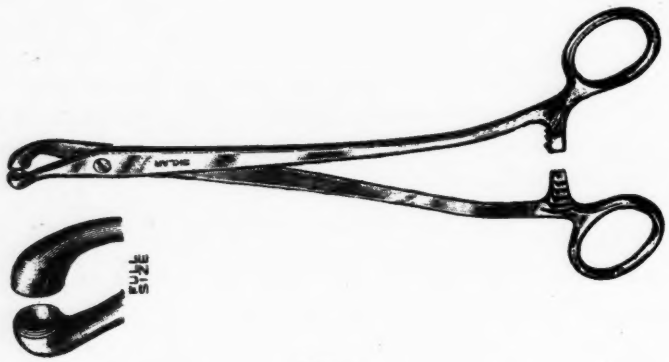

Fig. 1.

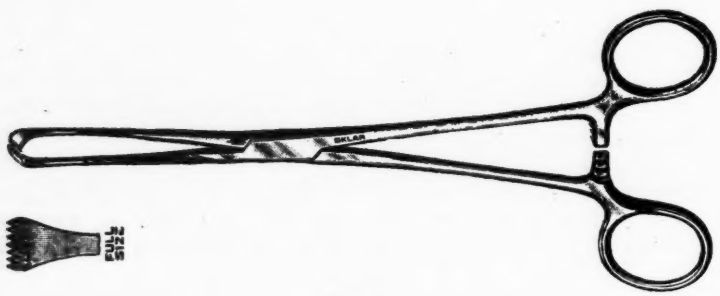

Fig. 2.

The cervix-grasping forceps, shown in Fig. 2, is used either as a tenaculum or for grasping tissue to be removed by means of a knife or scissors. The toothed extremities are similar to those of the Allis tissue forceps. The instrument is 8 inches long.

ESTRADIOL BUCCAL TABLETS IN THE TREATMENT OF THE MENOPAUSE

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ESTRADIOL has recently been made available for clinical use dissolved in a special polyethylene glycol wax base known to facilitate the absorption and utilization of steroid hormones when administered via the buccal route. In order to ascertain the relative dose of estradiol required by this method, fifty menopausal patients, who had previously been standardized on estradiol in some other form, were given tablets of this type.

Nineteen of these fifty patients had received estradiol benzoate intramuscularly one or two times a week; twelve patients had had a 25 mg. pellet of alpha-estradiol implanted subcutaneously; twelve patients had taken alpha-estradiol orally; and twenty-seven had been given ethinyl estradiol by mouth. In each instance, except with the pellet implants, the minimum effective dose of each preparation required to control the symptoms of the menopause was ascertained. Oral medications were given daily. Estradiol benzoate was injected one or two times each week, and the daily minimum effective dose calculated. Pellets were administered as 25 mg. of compressed alpha-estradiol and the daily dose was calculated on the basis of the number of days of relief from symptoms after pellet implantation. This is, of course, only a rough estimation which gives an average daily utilization. It would appear to be sufficiently accurate, however, for the purposes of this comparative investigation.

The accompanying table shows the results of this study. It is apparent that ethinyl estradiol is the most potent, weight for weight, of all the estradiol preparations studied. If the average daily dose for each form of estradiol is computed and these figures compared, ethinyl estradiol is seen to be six times as potent as estradiol benzoate by injection, alpha-estradiol by pellet implantation, and estradiol by buccal administration. It is of interest that the average daily minimum effective dose of these three substances is almost identical. Since all the pellets weighed 25 mg., it is likely that in some patients a smaller total amount would have been equally as effective. The minimum effective doses of estradiol benzoate by injection and estradiol by the buccal route are so similar that there seems to be little, if any, loss of estradiol when given buccally in this manner.

Approximately five times as much alpha-estradiol was required orally as by buccal absorption or by injection. This agrees with general experience, being due to the inactivation of estrogens by the liver. The buccal administration of steroids appears to avoid some of this destruction by circumventing the liver.

None of the fifty patients complained of nausea, although three reported that the buccal tablets took too long to dissolve and were therefore inconvenient to take. There was general agreement that the improvement in mood

TABLE I. DAILY DOSE IN MILLIGRAMS

MEDICATION		ESTRADIOL BENZOATE INTRA-MUSCULAR	ALPHA ESTRADIOL SUB-CUTANEOUS	ETHINYL ESTRADIOL ORAL	ALPHA ESTRADIOL ORAL	ESTRADIOL BUCCAL TABLETS BUCCAL
PATIENT	AGE					
T. D.	46			0.02		0.1
A. S.	49			0.05		0.25
D. B.	47			0.05		0.1
A. P.	32			0.05	1.0	0.25
A. H.	44			0.025		0.1
R. C.	47	0.24		0.05	1.5	0.25
E. K.	51			0.025	0.6	0.1
S. S.	39			0.025	1.0	0.25
L. M.	50	0.14		0.05		0.25
E. S.	50			0.02		0.1
K. S.	51	0.14				0.25
B. S.	46		0.16			0.1
D. M.	39			0.05		0.25
L. G.	44	0.09	0.14		0.5	0.1
E. Y.	45			0.02	0.8	0.2
S. S.	54			0.025		0.1
R. G.	47			0.025		0.25
E. F.	45			0.02		0.25
M. S.	38		0.12			0.25
G. W.	64	0.09				0.2
B. S.	45	0.05				0.2
S. G.	41		0.14	0.025		0.25
O. B.	40	0.05				0.1
S. J.	43			0.02	0.5	0.2
M. L.	50		0.16			0.1
M. K.	42			0.025		0.2
E. S.	48	0.14				0.25
M. H.	46		0.14		1.0	0.25
E. R.	52			0.025	0.5	0.1
M. Y.	52	0.09				0.1
M. P.	45			0.02		0.1
D. E.	50		0.1			0.1
B. A.	45			0.02		0.1
T. C.	46		0.14			0.25
S. K.	52		0.1	0.02		0.1
D. W.	46		0.14			0.25
H. S.	48			0.025	1.0	0.1
C. N.	55	0.09		0.025		0.1
S. R.	42		0.14			0.1
N. P.	42	0.24				0.25
S. T.	35	0.24				0.25
E. H.	40			0.02	0.6	0.1
R. T.	48	0.14		0.05	1.0	0.25
A. D.	51	0.14				0.25
S. R.	47	0.24				0.25
M. A.	38	0.09		0.01		0.1
E. R.	49	0.14				0.25
M. S.	38	0.14				0.1
M. C.	43		0.14			0.1
H. C.	54	0.14				0.1
Average daily dose		0.14*	0.135*	0.029	0.83	0.17

*Calculated.

from buccal tablets was equal to that from injections and pellets, and superior to that received from ethinyl estradiol. The tablets generally required from thirty to fifty minutes to dissolve. The three patients mentioned before reported one and one-quarter, one and one-half, and two hours for tablet absorption. These patients also needed higher than average dosages. Whether there is any connection between the slow absorption and high dosage requirement is difficult to say.

Dentures do not seem to influence the absorption rate significantly, although the time required for patients with complete dental plates was on the average somewhat longer than the mean.

No information was obtained regarding the incidence of withdrawal bleeding with the buccal tablets. This was in part due to the fact that sixteen patients were hysterectomized, and twelve patients were bleeding irregularly prior to therapy. This left only twenty-two patients in whom pertinent observations could be made. Two of these twenty-two patients reported vaginal staining, but this group is too small for valid statistical conclusions.

Summary

In this study of fifty menopausal women, the daily minimum effective dose of estradiol by the buccal route was essentially the same as that given intramuscularly as estradiol benzoate, or by pellet subcutaneously as compressed alpha-estradiol. One-sixth of this dose was required as ethinyl estradiol but five times as much was needed as alpha-estradiol when given orally.

There were no untoward reactions reported to the buccal estradiol tablets by any of the fifty menopausal patients, and these tablets were generally preferred to other types of previously administered oral estrogens.

Conclusions

The dose of estradiol required to control the symptoms of menopause, when administered as the buccal tablet, is approximately the same as that needed when given intramuscularly. Because of its low toxicity, ease of administration, and estrogenic potency, the buccal tablet of estradiol is a valuable therapeutic agent for the treatment of the menopause.

Through the kindness of Drs. Edward Henderson and William H. Stoner of Schering Corporation, estradiol benzoate was made available for this study as Progynon-B, ethinyl estradiol as Estinyl, alpha-estradiol tablets as Progynon-DH, as well as alpha-estradiol pellets and estradiol buccal tablets.

Imerman, Harold M.: Pellet Implantation With Alpha Estradiol for the Relief of the Menopausal Syndrome, West. J. Surg., p. 29, Jan., 1949.

Estrogen in the form of alpha estradiol pellet implantation is considered by the author to be satisfactory treatment for symptoms of the climacteric. It has the advantage over the parenteral administration in that one implantation results in a sustained absorption and prolonged relief of the symptoms. Full effect of the pellet as shown by vaginal smear is apparent in one month. At the height of absorption 8 to 10 rat units of estrogen can be recovered from twenty-four-hour urine. The follicle-stimulating hormone usually disappears from the urine between the second and fourth week following implantation. Pellets containing 25 mg. of alpha estradiol were used. The technique of pellet insertion is simple. Intradermal Novocain is placed at a selected site in the skin covering the lower abdomen, a stab wound is made with the sharp edge of a scalpel, and a Kearns pellet injector inserted down to the fascia. The pellet is inserted through the injector with a blunt stylet.

Symptoms are usually controlled for a period of five to seven months by a single pellet insertion. WILLIAM BICKERS.

Department of Reviews and Abstracts

Selected Abstracts

Anatomy, Anomalies

Bryan, Allen L., Nigro, Joseph A., and Counseller, Virgil S.: One Hundred Cases of Congenital Absence of the Vagina, Surg., Gynec. & Obst. **88**: 79, 1949.

The authors present comparative data on reconstruction of the congenitally absent vagina. A short summary of the various methods of reconstruction is given. The authors' series includes fourteen operations performed with transplanted bowel, seventy using split skin grafts, and fourteen employing the prolonged insertion of a nonirritating mold. In the last group the results were uniformly good, showing no mortality and a minimal morbidity. The authors feel that grafting is usually not necessary. The use of intestinal transplants is accompanied by high mortality, excessive discharge, and great morbidity.

L. M. HELLMAN.

Vernaglia, John B.: Double Uterus With Horn Menstruating Into the Abdomen, New England J. Med., p. 732, Nov. 11, 1948.

This report deals with a rare anomaly of the uterus. An extensive review of the literature did not reveal a similar case, which is that of a completely separated double uterus, both halves well developed, in which one uterus did not communicate with the vagina, but menstruated into the abdomen, retroperitoneally.

The situation was recognized at the time of the patient's third menstrual period, and a hemihysterectomy was performed. This patient later bore a child, delivered by cesarean section.

The subject of uterine anomalies is reviewed, with special reference to embryology, classification, etiology, complications, and treatment.

Conservative surgical treatment is emphasized. JAMES P. MARR.

Anesthesia, Analgesia

Kelly, Albert J.: Shock During Continuous Caudal Anesthesia, Anesth. & Analg. **27**: 236, 1948.

Shock has rarely been observed in continuous caudal anesthesia in obstetrics; in 604 patients delivered under continuous caudal anesthesia, shock in various degrees occurred in three cases. Two of these cases are reported in which cesarean section was done. Several errors made in the administration of the anesthesia in these two cases contributed to the development of shock. In the first place, a prophylactic dose of ephedrine was not given before operation; according to Hingson, this should be done in all cases with a systolic blood pressure below 150 mm. Insufficient time was allowed between the second and third doses of Metycaine to establish the level of anesthesia accurately. Metycaine

was injected under too great pressure and too rapidly; in the use of caudal anesthesia in obstetrics, it must be remembered that less pressure is required in caudal injections in women than in men. There is no way of measuring the amount of pressure employed, but experience in estimating the amount of the drug and the rate of injection necessary to obtain the desired level of anesthesia is quickly gained. In one of the cases reported, the abdomen may have been opened too soon after the second injection of Metycaine and the incision of the parietal peritoneum may have been a contributing factor in shock.

Further experience with caudal anesthesia in cesarean section has convinced the author that it is not necessary to have the skin anesthesia more than one inch above the umbilicus, if the patient is prepared psychologically and her fears allayed. This level of anesthesia can be obtained with 35 to 45 c.c. of 1.5 per cent Metycaine injected into the peridural space, with little danger of shock, no impairment of uterine contractions after delivery, and reduced blood loss. HARVEY B. MATTHEWS.

Mammary Glands

Lowenhaupt, Elizabeth, and Steinback, Howard L.: Clinical Response of Metastatic Lesions of Carcinoma of the Female Breast to Hormonal Therapy as Related to Histologic Grade of Malignancy, Surg., Gynec. & Obst. **88:** 291, 1949.

The authors discuss the hormonal treatment of twenty-seven cases of far-advanced breast carcinoma associated with metastases. These tumors were graded pathologically according to the criteria of Greenough. Seventeen cases were treated with estrogens while ten received testosterone. The response to therapy was judged by the effect on the metastases. With both types of therapy the response seems to be correlated with the histologic grading of the malignant tumors, those of the low grading responding most favorably. Inasmuch as there was not a sufficient number of low-grade tumors present, no definite conclusions can be drawn from this paper. L. M. HELLMAN.

Endocrinology

Kimbrough, Robert A., and Israel, S. Leon: The Use and Abuse of Estrogen, J. A. M. A. **138:** 1216, Dec. 25, 1948.

The authors quote three broad uses of estrogen, to achieve growth of all or part of the genital tract, to depress temporarily the function of the anterior lobe of the hypophysis, and to effect an antiandrogenic action. The most prevalent abuse in the usage of estrogen is the prescription of a routine daily dose to be taken more or less indefinitely. Another abuse is to consider all postmenopausal bleeding following estrogen therapy as withdrawal bleeding; to fail to do a curettage on these patients is sheer neglect. Estrogen should be avoided in postmenopausal menstrual irregularities. It should be avoided in cases of residual endometriosis. It should be avoided in cases where the individual gives a background of carcinoma, in cases of benign palpable tumors (breast, uterus), and also in cases of hepatic insufficiency. WILLIAM BERMAN.

Hepp, J. A.: Improper Use of Estrogens in Gynecology, Pennsylvania M. J. **52:** 379, 1949.

A study is reported of 52 patients who had been given estrogen without a thorough pelvic examination: 38 of these patients were in the menopausal group and the chief symptom in this group was irregular bleeding. Of the 14 patients in the nonmenopausal group, two who had been given stilbestrol for secondary amenorrhea were found to be pregnant. There were four cases in which malignancy was found—three cases of cancer of the cervix and one case of adenomatous polyp with beginning malignant degeneration; and there were five cases of uterine myomas. Five of the patients were radium castrates. From his study of this series of cases, the author concludes that estrogen therapy should

not be employed until the patient has been given a comprehensive general physical examination and a thorough pelvic examination. Hysterectomy, without removal of ovarian tissue, is not an indication for estrogen therapy. Estrogen therapy should be avoided in radium castrates, in endometriosis, and in cases of fibromyomas of the uterus. It is contraindicated if cancer is present, and also for patients with a family history of cancer. Estrogen therapy should be used only on definite indications; in the climacteric, when the therapy is indicated, it should always be interrupted by rest periods between courses of treatment. Patients should not be allowed to have prescriptions for estrogen refilled except on order of the doctor. HARVEY B. MATTHEWS.

Gordon, Israel: The Origin of Placental Trophoblast and the Function of Placental Gonadotrophin, The Lancet, p. 807, May 14, 1949.

For over fifty years it has been accepted that the invasive element of the mammalian placenta is of fetal origin, arising from the outermost covering of the blastocyst. The author offers the original theory that granulosa cells of the corona radiata accompany the ovum to the implantation site, and form the invasive cytotrophoblast. In a most detailed exposition of this thesis Dr. Gordon reinterprets embryologic, endocrinologic, pathologic, and phylogenetic observations selected from 102 articles bearing on the subject. Trophoblast can form where there is no embryo, can live after the embryo has died, and is found where there could never have been a fertilized ovum (chorionepithelioma in men). Trophoblast mimics maternal tissues in secreting steroid hormones. In the early stages of imbedding it is morphologically dissimilar to the lining of the blastocyst. These and other arguments are analyzed in detail, and lines of experimentation are suggested. That "chorionic" gonadotrophin is actually a product of the decidua is offered as a corollary.

IRVING L. FRANK.

Gynecology

Randazzo, M.: Allergic Phenomenon From Intravaginal Application of Penicillin and Sulfonamides, Quaderni Clin. ostet. e ginec. 3: 371, 1948.

The author reviews the literature on allergic states resulting from topical applications of penicillin and sulfonamides. He describes a severe urticarial reaction following the intravaginal use of penicillin for senile vaginitis and concludes that topical application of chemotherapeutic agents and antibiotic agents is not without hazards.

FRANK A. GRACEFFO.

Vecchietti, G.: The Autopurification of the Vagina. The Biological Significance of Lysozyme in the Vagina, Quaderni Clin. ostet. e ginec. 3: 73, 1948.

A vast field in the biology of the vagina is that which deals with autopurification. The intact, healthy vagina is capable of defending itself against a multiple variety of pathogenic organisms, whether they are artificially or naturally introduced.

In addition to listing such protective barriers as the mucosa, abundance of leucocytes, antimicrobe action of the epithelial cells, acidity, etc., the author includes an elaborate work-up of lysozyme, discovered by Fleming in 1902. This bactericidal agent is found in the vaginal and amniotic fluids and also in cord blood. The author has found it even in the vaginal fluid of newborns.

It is increased in local inflammatory conditions, in pregnancy, and in the puerperium. The author studies several different pathological states and attempts to correlate the amount of vaginal lysozyme in these conditions. He attributes great biological value to lysozyme as a protective agent. FRANK A. GRACEFFO.

Seng, F., Cochrane, W. J., and Mack, F. G.: The Vesical Neck Syndrome in Women of Middle Age, Canad. M. A. J. 60: 39, 1949.

The authors describe their findings in 225 women hospitalized because of the "vesical neck syndrome," which includes urinary frequency, urgency, dysuria, terminal distress, terminal blood, and tenesmus. Most sufferers were at or beyond the climacteric, although one-fifth of the patients were in the childbearing years. The chain of symptoms was often initiated by exposure to cold, and remained chronic, sometimes for many years. Lesions were present in the anterior urethra (75.5 per cent of cases) vesical trigone and neck (72.9 per cent), bladder mucosa and wall (28.0 per cent), and elsewhere. The most common single lesion was contracted urethra (52 per cent). A variety of edematous, congestive, hyperplastic, granular, and inflammatory changes were found in other locations. In one-fifth of cases there was no evidence of infection or irritation.

The important etiologic factors are: (a) trauma, (b) chronic low-grade infection, (c) deficiency of vitamins A and C, and (d) low estrin level and relative androgen increase, causing a stimulation of the female homologues of the prostate gland. Treatment consists of (a) eradication of infection, (b) urethral dilatation, and (c) resection or fulguration of hyperplastic and granular lesions. IRVING L. FRANK.

Menopause

Finkler, Rita S.: The Effect of Vitamin E in the Menopause, J. Clin. Endocrinol. 9: 89, 1949.

Synthetic vitamin E (tablets Ephynal Acetate, Hoffmann-La Roche) was used for the treatment of menopausal symptoms in sixty-six women where estrogenic therapy was deemed inadvisable because of familial history of malignancy, previous treatment for mammary or pelvic malignancy, or the presence of so-called precancerous lesions. Dosage ranged from 20 to 100 mg. daily, with an average of 10 mg. three times a day. Therapy was continued for periods of ten days to seven months and was interspersed with periods of simulating placebo tablets to rule out psychologic influences.

Results interpreted according to subjective responses ranged from complete relief of symptoms to no relief, and were graded as excellent, good, fair, or unsatisfactory. Approximately one-half of the patients experienced complete relief or enough relief to be considered within the categories of excellent or good. About one-fourth of the group were considered to have had fair responses and the remainder had no relief. In the latter group, the symptoms of five patients were aggravated. Two patients in the unsatisfactory group experienced side effects mainly as ocular symptoms. No effects were noted in the breasts, uterus, or vaginal epithelium during vitamin E therapy. Synthetic vitamin E was deemed a valuable aid in the treatment of menopausal patients in whom estrogens are contraindicated. C. J. EHRENBERG.

Newborn

Vale, C. Fremont: Diaphragmatic Hernia in a Newborn: Surgical Repair, Harper Hosp. Bull. 6: 153, 1949.

An infant apparently normal at birth regurgitated practically all feedings and showed marked cyanosis after each attempt at feeding after the fourth day. X-ray examination showed a diaphragmatic hernia through the esophageal meatus, with the entire stomach above the diaphragm. At operation by the abdominal route, the hernia was closed and the stomach tacked to the diaphragm at the left of the hiatus. Thirteen days later, x-ray study showed the stomach entirely below the diaphragm and functioning normally; the infant developed normally during the next year. HARVEY B. MATTHEWS.

Siddall, R. S., and West, R. H.: Anemia in Babies Delivered by Cesarean Section and Its Possible Prevention, Harper Hosp. Bull. 6: 139, 1948.

Because of the death of an infant soon after delivery by cesarean section with exsanguination as the apparent cause, blood counts and hemoglobin determinations were made on 60 infants delivered by cesarean section on the day of delivery, and, in some instances also in the third day of life. In all but three cases blood counts and hemoglobin were within normal values for the newborn, and therefore comparatively high. In three cases both hemoglobin and red blood cells were below normal levels and the infants were pale and listless; the two most severely affected were given blood transfusions and all three recovered and were in satisfactory condition when discharged from the hospital. A review of the case records of these three cases showed that all the infants were at or near full term; the indications for cesarean section were, respectively, placenta previa, previous cesarean section, and fulminating toxemia. The mother who was delivered by cesarean section because of placenta previa was anemic at the time of delivery; the other two mothers showed no anemia. In all three cases, the incision into the uterus at the time of operation passed through the placenta. In two other cases in which the placenta was also incised at operation, the infants showed no anemia. One of the infants who was anemic was a double-ovum twin; the placenta of this infant had been cut through, but the placenta of the other twin had not been cut and this twin was not anemic. In the case of the infant who showed the most severe anemia, there was unusual difficulty and delay in extracting the child from the uterus. On the basis of these findings it is suggested that in the three cases in which the infants were anemic, the incisions through the placenta cut one or more large blood vessels with resulting rapid loss of blood from the fetal circulation. In the other two cases in which the placenta was cut through but the infant was not anemic, apparently no large vessels were cut and blood loss was slight. The possible danger to the infant from cutting through the placenta at the time of cesarean section should be recognized. HARVEY B. MATTHEWS.

Nobile, T.: Clinical Statistical Contributions to the Study of Neonatal Mortality, Ginecologia 14: 20, 1948.

The author studies 4,353 deliveries and reviews the various causes of neonatal mortality. The total incidence is found to be 4.26 per cent, 2.77 per cent occurring intrapartum and 1.49 per cent post partum. Prematurity is responsible for 45.6 per cent of these deaths, whereas the trauma of operative delivery with forceps, versions, and cesarean sections accounts for 12.8 per cent. Premature separation and placenta previa are followed by a 13 per cent neonatal mortality. Umbilical cord complications in different situations are responsible for 13.4 per cent. The remainder of inciting causes of neonatal mortality is divided among precipitous labors, prolonged narcosis from anesthesia, abnormal labors, and excessive birth weight incidental to pluriparity. FRANK A. GRACEFFO.

Complications of Pregnancy

Coppola, L.: Experimental Contributions to the Doctrine of Autointoxication in Pregnancy, Ginecologia 14: 212, 1948.

The author attempts to offer experimental evidence for a toxic proteolytic substance from the placenta as the etiological agent in toxemias of pregnancy. No controls are used and the results are rather dubious. Some interesting statistics are offered, however, on the importance of conservative management. Another point of note is the reduced incidence of toxemias during the war years, coincidental with diminished caloric intake.

FRANK A. GRACEFFO.

Caldwell, Renwick K.: Torsion of the Normal Fallopian Tube Complicating Pregnancy, New England J. Med. 240: 421, 1949.

This unusual obstetrical complication reported from the Green Mountain Clinic and Dartmouth Medical School, Hanover, New Hampshire, is that of a young primigravida, between the fifth and sixth months of her otherwise uneventful pregnancy, developing severe localized pain in the right lower quadrant and right flank.

An exploratory laparotomy revealed a tubal mass 4 by 3 cm., which was excised and proved to be the twisted terminal two thirds of the right Fallopian tube.

A pathological examination revealed congestion and hematosalpinx, the result of torsion of the right tube.

Following the operation the pregnancy has progressed normally. JAMES P. MARR.

Taricco, G.: Uterine Fibromyomas in Pregnancy and in the Puerperium, Ginecologia 14: 257, 1948.

The author concludes that under exceptional circumstances pregnancy can occur and go to term even in uteri markedly deformed by voluminous fibroids. The average age incidence of fibroids complicating gestation is 36 years. The most serious consequences occur in elderly primigravidas. The most serious complication is necrobiosis, particularly occurring at the seventh and ninth months, when vascular and degenerative changes are most likely to occur.

The author reviews the literature and gives a good account of the pathogenesis of complications. His observations are illustrated by nine case reports of complications ranging from simple degenerative changes to complete intestinal obstruction resulting from necrosis in a twisted pedunculated fibroid during the puerperium. In addition, he makes a plea for careful observation and conservative surgical intervention whenever the latter is indicated. FRANK A. GRACEFFO.

Puerperium

Bigger, Joseph W.: The Aetiology and Prophylaxis of Puerperal Sepsis, Brit. M. J. 2: 4528, Oct. 18, 1947.

The subject, during the past 200 years, is reviewed by an authority in bacteriology and preventive medicine. Reference to the epidemics that were particularly devastating during the first part of this time is made. As the paper was presented upon the occasion of celebrating the 200th anniversary of the founding of the Rotunda Hospital, special mention is made of the early contributions of former masters such as Labatt (1814-1821) and Collins (1828-1833).

Great emphasis is placed upon the exogenous *Streptococcus pyogenes* type of infection. The methods of spread of this organism from the main reservoir in the upper respiratory tracts of patients and attendants is discussed at considerable length. The importance of segregation, isolation, and the availability of bacteriological facilities is stressed. The author points out the value of the contributions of Lancefield and Griffin in our present understanding of the pathogenicity of various strains of streptococci.

Considerably less attention is directed to infections caused by *Clostridium welchii,* and the *Staphylococcus pyogenes.* The problem of endogenous infections and contamination from the intestinal tract is discussed briefly. He considers the employment of the instillations of antiseptic agents into the vagina as a routine but does not favor such measures.

The author closes with a warning that the young obstetricians of the present day may not have an opportunity of observing parturients with serious infection because of the extensive precautions now exercised. Lack of clinical experience then may, according to Dr. Bigger, tend to cause a relaxation of elaborate, time-consuming, and sometimes irritating precautions with the sudden reappearance of infection, if *Str. pyogenes* continues to exist in the throats of attendants. R. GORDON DOUGLAS.

Hesseltine, H. Close: Streptomycin and Penicillin in Febrile Obstetric and Gynecologic Conditions, Illinois M. J., p. 156, March, 1949.

This presentation briefly reviews the various causes for the declining incidence of postpartum and postoperative pelvic infections and the role played by antibiotic agents.

A tabulation of the efficiency of these agents in combating various organisms and disease entities is offered and illustrative cases of great benefit from these agents outlined. The author stresses the importance of use of antibiotics in sufficient amount and for adequate time intervals, and also by the parenteral route for the proper result.

In considering the prophylactic value of these agents as used at the Chicago Lying-in Hospital, it would appear from the short series presented that advances in aseptic technique and adjuvant methods of blood and fluid replacements have been of greater importance in preventing pelvic infection than have the antibiotics which are discussed.

S. B. GUSBERG.

Blondet, C.: Treatment of Thrombosis and Thrombophlebitis in Obstetrics and Gynecology With Anticoagulants, Folia gynaec. 43: 265, 1948.

The author gives an account of the etiological factors in phlebothrombosis and thrombophlebitis and compares the different modes of therapy, stressing the use of heparin, dicumarol, and penicillin. An interesting point noted by the author is the use of anticoagulant therapy in uterine subinvolution on the supposition that a chronic passive congestion of the pelvic veins exists as a factor delaying involution.

ANDREW A. MARCHETTI.

Vaginal Infestations

Greenblatt, Robert B., Dienst, Robert B., Chen, Calvin, and West, Robert: Oral Aureomycin in the Therapy of Streptomycin-Resistant Granuloma Inguinale, South. M. J. 41: 1121, 1948.

Granuloma inguinale continues to be a major venereal scourge of the Southern states. Streptomycin in a dose of 4 Gm. per day for five days proved to be satisfactory treatment in 138 patients. About 10 per cent relapsed and one-half of these responded well to a second course of treatment.

There were four cases which were streptomycin resistant. These were treated on varying dose schedules of intramuscular aureomycin to which each failed to respond. They were then placed upon 250 mg. capsules of aureomycin four times daily to a total dose of 5,000 mg. The lesions in two patients healed completely. The others had a residual small area of infection from which occasional Donovan bodies could be demonstrated. It would appear that oral aureomycin with its low toxicity may be the long-sought solution to the treatment of granuloma inguinale.

WILLIAM BICKERS.

Necrology

WILLIAM CLARK DANFORTH, B.S., M.D., obstetrician and gynecologist, died on Nov. 11, 1949, at the Evanston Hospital at the age of 71 years. Long a member of the Advisory Editorial Staff of the JOURNAL, he also contributed many valuable articles to its pages.

Dr. Danforth was born in Chicago in 1878, graduated from Northwestern University in 1900 and from its medical school in 1903, after which he spent two years in Vienna. He became professor of obstetrics and gynecology in his Alma Mater and later was made emeritus, as well as chief of service at the Evanston Hospital.

A Life Fellow of the American Gynecological Society, Dr. Danforth served as President in 1942. He was also a Diplomate of the Board and a Fellow of the American College of Surgeons. Of interest is the fact that he was of the fourth generation of his family in the medical profession, his father being a founder of the Wesley Memorial Hospital in Chicago. A son, Dr. David N. Danforth, survives.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Joseph Baer. *Secretary,* Norman F. Miller, 1313 East Ann St., Ann Arbor, Mich. Next meeting, May 11, 12, 13, 1950, The Greenbrier, White Sulphur Springs, Va.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* Samuel A. Cosgrove, Jersey City, N. J. *Secretary,* L. A. Calkins, University of Kansas Medical Center, Kansas City 3, Kansas. Annual meeting Hot Springs, Va., September 7, 8, 9, 1950.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Lawrence M. Randall, Rochester, Minn. *Secretary-Treasurer,* John I. Brewer, 24 West Ohio St., Chicago 10, Ill. Annual meeting to be held Thursday, Friday, and Saturday, Sept. 21, 22, and 23, 1950, at the Hotel Schroeder, Milwaukee, Wis.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* C. J. Andrews, Norfolk, Va. *Secretary,* E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Next meeting, Feb. 9, 10, and 11, 1950, Hotel Roanoke, Roanoke, Va.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* James R. Blos, Huntington, W. Va. *Secretary,* A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June 19-26, 1950, San Francisco, Calif.

New York Obstetrical Society. (1863) *President,* R. Gordon Douglas. *Secretary,* Charles M. McLean, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* Newlin F. Paxson. *Secretary,* George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* Eugene A. Edwards. *Secretary,* Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* William T. Daily. *Secretary,* J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Houston S. Everett. *Secretary-Treasurer,* W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Edward Friedman. *Secretary,* Lester J. Bossert, 2404 Auburn Ave., Cincinnati 19, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Rudy F. Vogt. *Secretary-Treasurer,* Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Ronald Frazier. *Secretary-Treasurer,* Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* R. A. D. Gillis. *Secretary,* Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.

Obstetrical Society of Boston. (1861) *President,* M. Fletcher Eades. *Secretary,* H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Arthur E. G. Edgelow, Springfield, Mass. *Recorder,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Philip H. Arnot. *Secretary-Treasurer,* R. Glenn Craig, 490 Post St., San Francisco, Calif.

Washington Gynecological Society. (1933) *President,* George Nordlinger. *Secretary,* Stafford W. Hawken, 1150 Connecticut Ave., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Conrad G. Collins. *Secretary,* E. W. Nelson, 1407 S. Carrollton Ave., New Orleans, La. Meetings held October, November, January, March, and May.

***Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.**

St. Louis Gynecological Society. (1924) *President,* Matthew W. Weis. *Secretary,* Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo., Regular meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Donald Dallas. *Secretary,* Donald W. de Carle, 2000 Van Ness Ave., San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* Julius McIver, Dallas. *Secretary,* George F. Adam, 4115 Fannin St., Houston 4, Tex. Annual meeting, Dallas, Texas, September, 1949.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* O. W. Picard. *Secretary,* Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Gynecologists and Obstetricians. (1938) *President,* Louis G. Fournier. *Secretary,* Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* Gilbert F. Douglas. *Secretary,* Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Charles D. Kimball. *Secretary-Treasurer,* Robert K. Plant, 732 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.

Denver Gynecological and Obstetrical Society. (1942) *President,* Lyman W. Mason. *Secretary-Treasurer,* Jack M. Simmons, Jr., 638 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Henry A. Sincock. *Secretary-Treasurer,* Edith McCann, 425 East Wisconsin Ave., Milwaukee 2. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* D. Dalton Deeds. *Secretary,* Jesse A. Rust, Jr., 3115 University Ave., San Diego 4, Calif. Meetings held on the last Friday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* H. A. Wheeler, Grand Forks. *Secretary,* C. B. Darner, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* Walter McMann. *Secretary-Treasurer,* L. L. Shamburger, State Health Department, Richmond, Va. Next meeting not announced.

Columbus Obstetric and Gynecologic Society. (1944) *President,* Wayne Brehm. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.

Naussau Obstetrical Society. (1944) *President,* Robert S. Millen. *Secretary-Treasurer,* Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Charles W. Frank. *Secretary,* Benjamin Karen, 1100 Grand Concourse, New York 56, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* C. Wendell Knudson, Medical and Dental Bldg., Seattle, Wash. Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* Harold V. Holter. *Secretary,* William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* A. M. McCausland. *Secretary-Treasurer,* Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Wallace B. Bradford. *Secretary,* Richard B. Dunn. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* H. B. Atlee. *Secretary,* K. M. Grant. Annual meeting, June, 1950.

Akron Obstetrical and Gynecological Society. (1946) *President,* George A. Palmer. *Secretary-Treasurer,* Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.

Minnesota Obstetrical and Gynecological Society. *President,* Russell J. Moe. *Secretary,* John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President,* Homer L. Pearson. *Secretary,* John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

Omaha Obstetrical and Gynecological Society. (1947) *President,* Ralph Luikhart. *Secretary-Treasurer,* Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* John W. Records. *Secretary-Treasurer,* Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.

Cleveland Obstetrical and Gynecological Society. (1947) *President,* Robert E. Faulkner. *Secretary,* G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.

New Jersey Obstetrical and Gynecological Society. (1947) *President,* George B. German. *Secretary,* C. Norman Witte, Pt. Pleasant, N. J. Meetings semiannually.

Honolulu Obstetrical and Gynecological Society. (1947) *President,* K. S. Tom. *Secretary,* S. Nishijima, 1221 Victoria St., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.

Oregon Society of Obstetricians and Gynecologists. *President,* Gerald Kinzel. *Secretary-Treasurer,* Theodore M. Bischoff, 529 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.

National Federation of Obstetric-Gynecologic Societies. (1945) *President,* Ralph E. Campbell. *Secretary,* Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.

Dayton Obstetrical and Gynecological Society. (1937) *President,* Albert Hirsheimer. *Secretary,* Walter K. Gregg, Dayton, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.

Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) *President,* Asa A. Newsom. *Secretary,* A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.

Queens Gynecological Society. (1948) *President,* Edward C. Veprovsky. *Secretary,* George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.

Mississippi Association of Obstetricians and Gynecologists. (1947) *President,* R. A. Street, Jr. *Secretary,* William Weiner, Barnett-Madden Bldg., Jackson, Miss. Meetings held semiannually.

Florida Obstetrical and Gynecological Society. *President,* Charles J. Collins. *Secretary,* Dorothy D. Brame, Orlando, Fla. Next annual meeting, Belleair, April 10, 1949.

South Carolina Obstetrical and Gynecological Society. (1946) *President,* J. Decherd Guess. *Secretary,* Arthur L. Rivers, 231 Calhoun St., Charleston, S. C. Meetings held in spring and fall.

Buffalo Obstetrical and Gynecological Society. (1946) *President,* W. Herbert Burwig. *Secretary,* Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.

El Paso Gynecological Society. (1948) *President,* Gerald H. Jordan. *Secretary-Treasurer,* Gray E. Carpenter, 303 N. Oregon St., El Paso, Texas.

Kentucky Obstetrical and Gynecological Society. (1947) *President,* W. O. Johnson. *Secretary,* Edwin P. Solomon, 910 Heyburn Bldg., Louisville, Ky.

Indianapolis Obstetrical and Gynecological Society. (1947) *President,* David L. Smith. *Secretary,* Sprague H. Gardiner, 314 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.

Houston Obstetrical and Gynecological Society. (1939) *President,* John A. Wall. *Secretary-Treasurer,* Herman L. Gardner, Hermann Professional Bldg., Houston 5, Texas. Meetings held second Tuesday of each month except July, August, and September.

Iowa Obstetric and Gynecologic Society. *President,* J. H. Randall. *Secretary,* William C. Keettel, Iowa City, Iowa.